



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Abacavir (ABC, Ziagen) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Pediatric Oral Solution: 20 mg/mL

Tablets: 300 mg (scored)

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 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 counts for more than 6 months (24 weeks) on abacavir twice daily, dose can be changed from twice daily to once daily (see text below).

Weight Band Dosing (Weighing ≥14 kg)

| Weight (kg) | Scored 300-mg Tablet | | |
|---------------|----------------------|---------------------|----------------------|
| | Twice Daily AM Dose | Twice Daily PM Dose | Once Daily Dose |
| 14 to <20 kg | ½ tablet (150 mg) | ½ tablet (150 mg) | 1 tablet (300 mg) |
| ≥20 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).
- Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of abacavir; however, other studies have not substantiated this finding, and there are no data in children.

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.

- In patients who can be treated with pill formulations, therapy can be initiated with once-daily administration. If therapy was initiated with twice-daily liquid abacavir, then it can be changed from twice daily to once daily in clinically stable patients with undetectable viral load and stable CD4 cell counts (without decline) for more than 6 months (24 weeks) (see text below).

Adolescent (Weighing ≥ 25 kg) and Adult Dose:

- 300 mg twice daily or 600 mg once daily.

[Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weight ≥ 40 kg)/Adult Dose:

- One tablet twice daily.

[Epzicom] Abacavir plus Lamivudine

Adolescent (Weight ≥ 25 kg) and Adult Dose:

- One tablet once daily.

[Triumeq] Abacavir plus Dolutegravir plus Lamivudine

Adolescent (Weight ≥ 40 kg) and Adult Dose:

- One tablet once daily.

Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- 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 (CrCl) < 50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

Didanosine (ddl, Videx) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Videx Pediatric Powder for Oral Solution: Reconstituted 10 mg/mL

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

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

Tablets for Oral Suspension: 100 mg, 150 mg, and 200 mg

Dosing Recommendations

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

- 50 mg/m² 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/m² body surface area every 12 hours

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

- 120 mg/m² body surface area every 12 hours
- Dose range: 90–150 mg/m² body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naïve children ages 3–21 years, 240 mg/m² body surface area once daily (oral solution or capsules) has effectively resulted in viral suppression.

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

| Body Weight (kg) | Dose (mg) |
|------------------|-------------------|
| 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 (kg) | Dose (mg) |
|------------------|-------------------|
| <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 TDF 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 and tablets for oral suspension contain 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.
- If using tablets for oral suspension: Tablets are not to be swallowed whole. For full

Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate (TDF):

- This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic non-response, high rates of early virologic failure and rapid selection of resistance mutations ([Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)).

therapeutic effect, 2 tablets may be chewed or dispersed in water before administration. To disperse tablets: add 2 tablets to at least 1 ounce (30 mL) of water. Drink entire dispersion immediately. For children 1 or 2 tablets may be chewed or dispersed in water before administration.

Metabolism/Elimination

- Renal excretion 50%
- 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 July 10, 2017; last reviewed July 10, 2017)

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

Formulations

Pediatric Oral Solution: 10 mg/mL

Capsules: 200 mg

Generic Formulations: None available

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

Dosing Recommendations

Neonatal/Infant Dose (Aged 0 to <3 Months)

Oral Solution:

- 3 mg/kg once daily.

Note: Please see [Special Considerations for Neonates](#) section.

Pediatric Dose (Aged ≥3 Months to 17 Years)

Oral Solution:

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

Capsules (Weight >33 kg):

- 200 mg once daily.

Adolescent (Aged ≥18 Years)/Adult Dose

Oral Solution for Those Unable to Swallow Capsules:

- 240 mg (24 mL) once daily.

Capsules:

- 200 mg once daily.

Combination Tablets

[Truvada tablet] Emtricitabine plus TDF

Selected Adverse Events

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

Special Instructions

- Although emtricitabine can be administered without regard to food, food requirements vary depending on the other ARV drugs contained in a combination tablet. For Atripla (administer without food) and Complera (administer with a meal of at least 500 calories), refer to efavirenz or rilpivirine special instructions.
- 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.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.
- Before using emtricitabine, screen patients for HBV.

Metabolism/Elimination

- Limited metabolism: No cytochrome P (CYP) 450 interactions.

Truvada Tablets Dosing Table

| Body Weight kg | FTC/TDF Tablet Once Daily |
|--|------------------------------|
| 17 to <22 | One 100 mg/150 mg tablet |
| 22 to <28 | One 133 mg/200 mg tablet |
| 28 to <35 | One 167 mg/250 mg tablet |
| Adolescent (Weighing \geq 35 kg) and Adult Dose | One 200 mg/300 mg tablet |

[Descovy] Emtricitabine plus TAF

Adolescent (Weighing $>$ 35 kg) and Adult Dose:

- 1 tablet once daily

[Atripla] Efavirenz plus Emtricitabine plus TDF 300 mg

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

- 1 tablet once daily.
- Administer without food.
- See efavirenz section for pregnancy warning.

[Complera] Emtricitabine plus Rilpivirine plus TDF

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

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

[Odefsey] Emtricitabine plus Rilpivirine plus (TAF)

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

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment (ART) history with HIV-1 RNA \leq 100,000 copies per mL; or to replace a stable ART regimen in those who are 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

Adult Dose (Aged \geq 18 Years):

- 1 tablet once daily in treatment-naïve or virologically suppressed adults.
- Administer with a meal.

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

- Renal excretion 86%: Potential competition with other compounds that undergo renal elimination.
- Dosing of emtricitabine in patients with renal impairment: Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with creatinine clearance (CrCl) $<$ 50 mL/min or in patients requiring dialysis.
- Do not use Truvada (fixed-dose combination) in patients with CrCl $<$ 30 mL/min or in patients requiring 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 be increased 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 in patients with estimated CrCl below 30 mL per minute.

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

- 1 tablet once daily with food in ART-naive patients or to replace the current ART regimen in those who are virologically suppressed (i.e., 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.

Lamivudine (3TC, Epivir) (Last updated April 27, 2017; last reviewed April 27, 2017)

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^a)

Tablets: 150 mg (scored) and 300 mg (generic); 100 mg (Epivir HBV^a)

Fixed-Dose Combination Tablets:

- [*Combivir and generic*] Lamivudine 150 mg plus zidovudine 300 mg
- [*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

Tablets: 100 mg, 150 mg, and 300 mg

Dosing Recommendations

Neonate and Infant Dose (Birth to <4 Weeks):

- 2 mg/kg twice daily

Note: Please see [Infant ARV Prophylaxis in the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States](#) for dosing used to prevent perinatal transmission.

Pediatric Dose (Aged ≥4 Weeks):

- 4 mg/kg (up to 150 mg) twice daily
- In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine is not generally recommended. Please refer to text for more detail.

Weight-Band Dosing (Weighing ≥14 kg)

Scored 150 mg tablet

| Weight | Twice-Daily AM Dose | Twice-Daily PM Dose | Once-Daily Dose |
|---------------|---------------------|---------------------|--------------------|
| 14 to <20 kg | ½ tablet (75 mg) | ½ tablet (75 mg) | 1 tablet 150 mg |
| ≥20 to <25 kg | ½ tablet (75 mg) | 1 tablet (150 mg) | 1½ tablets 225 mg |
| ≥25 kg | 1 tablet (150 mg) | 1 tablet (150 mg) | 2 tablets (300 mg) |

Selected Adverse Events

- Minimal toxicity
- 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.

Metabolism/Elimination

- **Renal excretion:** Dosage adjustment required in renal insufficiency.
- Fixed-dose combination tablets should not be used in patients with creatinine clearance <50 mL/min, on dialysis, or with impaired hepatic function.

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged ≥ 3 years with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 T lymphocyte count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily.

Adolescent and Adult Dose:

Weighing <25 kg:

- 4 mg/kg (up to 150 mg) twice daily

Weighing ≥ 25 kg:

- 150 mg twice daily or 300 mg once daily

[Combivir and Generic] Lamivudine/Zidovudine

Adolescent (Weighing ≥ 30 kg)/Adult Dose:

- 1 tablet twice daily

[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

Adolescent (Weighing ≥ 40 kg)/Adult Dose:

- 1 tablet twice daily

[Epzicom] Abacavir/Lamivudine

Adolescent (Weighing ≥ 25 kg)/Adult Dose:

- 1 tablet once daily

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Adolescent (Weighing ≥ 40 kg)/Adult Dose:

- 1 tablet once daily

Stavudine (d4T, Zerit) (Last updated April 27, 2017; last reviewed April 27, 2017)

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, 40 mg

Dosing Recommendations

Neonate/Infant Dose (Birth to 13 Days):

- 0.5 mg/kg per dose twice daily

Pediatric Dose (Aged ≥ 14 Days and Weighing < 30 kg):

- 1 mg/kg per dose twice daily

Adolescent (≥ 30 kg)/Adult Dose:

- 30 mg per dose twice daily

Selected Adverse Events

- Mitochondrial toxicity, **highest risk of all NRTI drugs**
- Peripheral neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a 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 nucleoside reverse transcriptase inhibitors). The risk is increased when 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, Genvoya) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

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

Dosing Recommendations

Combination Tablets

[Descovy] Emtricitabine 200 mg plus TAF 25 mg

Pediatric/Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- 1 tablet once daily

[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

Pediatric/Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- 1 tablet once daily with food in antiretroviral (ARV) treatment-naive patients or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA < 50 copies/mL) and 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 ≥ 35 kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no ARV treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 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.

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 use of 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.
- If using Descovy please see the [Emtricitabine](#) section of the drug appendix.
- If using Genvoya please see the [Elvitegravir](#), [Emtricitabine](#), and [Cobicistat](#) sections of the drug appendix for additional information.
- Use of Genvoya is not recommended with other ARV drugs.
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or protease inhibitors co-formulated with cobicistat.
- When using Odefsey, refer to the [Emtricitabine](#) and [Rilpivirine](#) sections of the drug appendix. 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).

Pharmacology

- TAF undergoes renal excretion.
- Dosing in patients with renal insufficiency: TAF-containing formulations are not recommended in patients with estimated creatinine clearance below 30 mL per minute.

- TAF-containing formulations do not require dosage 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.

Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 = 1 g oral powder; supplied with dosing scoop)

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

Dosing Recommendations

Neonate/Infant Dose:

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

Pediatric Dose (Aged ≥2 Years to <12 Years)^a:

- 8 mg/kg/dose once daily

TDF Oral Powder Dosing Table

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

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 antiretroviral (ARV) drugs contained in a combination tablet.

TDF Tablet Dosing Table
(Aged ≥ 2 Years and Weighing ≥ 17 kg)

| Body Weight kg | TDF Tablet Once Daily |
|-------------------|--------------------------|
| 17 to <22 | 150 mg |
| 22 to <28 | 200 mg |
| 28 to <35 | 250 mg |
| ≥ 35 | 300 mg |

Adolescent (Weighing ≥ 35 kg)^a and Adult Dose:

- TDF 300 mg once daily

Combination Tablets

[Truvada] Emtricitabine plus TDF

Truvada Tablets Dosing Table

| Body Weight kg | FTC/TDF Tablet Once Daily |
|----------------------------------|----------------------------------|
| 17 to <22 | One FTC 100 mg/TDF 150 mg tablet |
| 22 to <28 | One FTC 133 mg/TDF 200 mg tablet |
| 28 to <35 | One FTC 167 mg/TDF 250 mg tablet |
| ≥ 35 (Adolescent and Adult) | One FTC 200 mg/TDF 300 mg tablet |

[Atripla] Efavirenz plus Emtricitabine plus TDF

Adolescent (Aged ≥ 12 years and 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, with no history of virologic failure, resistance to rilpivirine and other ARV drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 400 calories.

[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

Adolescent (Weighing > 35 kg) and Adult Dose:

- 1 tablet once daily in treatment-naïve adults or to replace the current ARV regimen in those who are 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 Stribild.
- Administer with food.

For Atripla (administer without food) and Complera (administer with a meal of at least 400 calories), refer to efavirenz or rilpivirine special instructions, respectively.

- 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 clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir and cobicistat sections of the drug appendix for additional information.

Metabolism/Elimination

- Renal excretion
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function (creatinine clearance < 50 mL/min). Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
- Atripla and Complera (fixed-dose combinations) should not be used in patients with CrCl < 50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl < 30 mL/min or in patients requiring dialysis.
- 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.

^a See text for concerns about decreased BMD, especially in pre-pubertal patients and those in early puberty (Tanner Stages 1 and 2).

Zidovudine (ZDV, AZT, Retrovir) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 (IV) 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
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

Dosing Recommendations

| Recommended Neonatal Dose for Treatment of HIV ^a | | | | | | | | | |
|---|--|------------------|---|------------|------|------------|--------|------------|------|
| Weeks' Gestation at Birth | <p>Zidovudine Oral Dosing:</p> <ul style="list-style-type: none"> • Twice-Daily Dosing <p>Note: For infants unable to tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval.</p> | | | | | | | | |
| ≥35 Weeks' Gestation at Birth | <p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"> • 4 mg/kg orally twice daily or alternative simplified weight band dosing <p>Simplified Weight Band Dosing for Infants Aged ≥35 Weeks:</p> <p>Note: Provides approximately 4 mg/kg orally twice daily from birth to 4 weeks of age</p> <table border="1"> <thead> <tr> <th>Weight Band (kg)</th> <th>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th> </tr> </thead> <tbody> <tr> <td>2 to <3 kg</td> <td>1 mL</td> </tr> <tr> <td>3 to <4 kg</td> <td>1.5 mL</td> </tr> <tr> <td>4 to <5 kg</td> <td>2 mL</td> </tr> </tbody> </table> <p>Aged >4 Weeks:</p> <ul style="list-style-type: none"> • 12 mg/kg orally twice daily | Weight Band (kg) | Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily | 2 to <3 kg | 1 mL | 3 to <4 kg | 1.5 mL | 4 to <5 kg | 2 mL |
| Weight Band (kg) | Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily | | | | | | | | |
| 2 to <3 kg | 1 mL | | | | | | | | |
| 3 to <4 kg | 1.5 mL | | | | | | | | |
| 4 to <5 kg | 2 mL | | | | | | | | |
| ≥30 to <35 Weeks' Gestation at Birth | <p>Birth to Age 2 Weeks:</p> <ul style="list-style-type: none"> • 2 mg/kg orally twice daily <p>Aged 2 Weeks to 6 to 8 Weeks:</p> <ul style="list-style-type: none"> • 3 mg/kg orally twice daily <p>Aged >6 to 8 Weeks:</p> <ul style="list-style-type: none"> • 12 mg/kg orally twice daily | | | | | | | | |

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) 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.

Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal

| Recommended Neonatal Dosing for Treatment of HIV^a | |
|---|--|
| <30 Weeks' Gestation at Birth | <p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"> • 2 mg/kg orally twice daily <p>Aged 4 Weeks to 8 to 10 Weeks:</p> <ul style="list-style-type: none"> • 3 mg/kg orally twice daily <p>Aged >8 to 10 Weeks:</p> <ul style="list-style-type: none"> • 12 mg/kg orally twice daily |

^a For prevention of perinatal transmission see [Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#).

Infant/Child Dose (Age ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery with Body Weight ≥4 kg):

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/m² body surface area every 12 hours

Adolescent (Aged ≥18 Years) and Adult Dose:

- 300 mg twice daily

[Combivir and Generic] Lamivudine plus Zidovudine

Adolescent (Weight ≥30 kg) and Adult Dose:

- 1 tablet twice daily

[Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weight ≥40 kg) and Adult Dose:

- 1 tablet twice daily

insufficiency.

- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use fixed-dose combination products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min, on dialysis, or who have impaired hepatic function.

Efavirenz (EFV, Sustiva) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Dosing Recommendations

Neonatal Dose:

- Efavirenz is not approved for use in neonates.

Pediatric Dose:

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

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that efavirenz generally not be used in children aged 3 months to <3 years. If use of efavirenz is unavoidable due to the clinical situation, the Panel suggests the use of investigational doses of efavirenz in this age group. See text for investigational dosing tables; evaluation of CYP 2B6 genotype is required prior to use. Therapeutic drug monitoring should be considered with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure at age 3 years after making the transition to the new dose (see text under therapeutic drug monitoring at the bottom of this section). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

Children Aged ≥ 3 Years and Weighing ≥ 10 kg:

Note: See Tables 1a and 1b in text for recommended dosing if EFV must be used in children aged <3 years

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, 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. Consider alternatives to efavirenz when co-administered with a drug with known risk of *Torsades de Pointes* or when administered to patients at higher risk of *Torsades de Pointes*

Special Instructions

- Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Administer whole capsule or tablet of Atripla on an empty stomach. Avoid administration with a high-fat meal because of potential for increased absorption.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.
- Efavirenz should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

Administer Efavirenz Once Daily

| Weight (kg) | Efavirenz Dose (mg) ^{a,b} |
|-------------------|------------------------------------|
| 10 kg to <15 kg | 200 mg |
| 15 kg to <20 kg | 250 mg |
| 20 kg to <25 kg | 300 mg |
| 25 kg to <32.5 kg | 350 mg |
| 32.5 kg to <40 kg | 400 mg |
| ≥40 kg | 600 mg |

^a The dose in mg can be dispensed in any combination of capsule strengths.

^b Some experts recommend a dose of 367 mg/m² body surface area (maximum dose 600 mg) because of concern for under-dosing, especially at the upper end of each weight band (see Pediatric Use for details).

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 600 mg once daily

[Atripla] Efavirenz plus Emtricitabine plus TDF

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

Adult Dose:

- One tablet once daily

Instructions for Use of 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*.
- Dosing of efavirenz in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product and TDF and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers at higher risk of toxicity (see text for information about therapeutic drug monitoring for management of mild or moderate toxicity).

Etravirine (ETR, Intelence, TMC 125) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 Kilogram (kg) | 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 |

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.
- Patients unable to swallow etravirine tablets may disperse the tablets in liquid, as follows: 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.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

- Dosing of etravirine in patients with renal impairment: Dose adjustment is not required in patients with renal impairment.

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.
- Multiple interactions with antiretroviral agents and other drugs (see text below)

Nevirapine (NVP, Viramune) (Last updated April 27, 2017; last reviewed April 27, 2017)

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: No longer available in the United States

Dosing Recommendations

Neonate/Infant Dose (≤ 14 Days) for Prevention:

- See [Infant Antiretroviral Prophylaxis and Neonatal Antiretroviral Drug Dosing](#) of the [Perinatal Guidelines](#) for dosing.

Treatment of HIV Infection:

Pediatric Dose: Immediate Release and Suspension Formulations

- In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of enzymes involved in its metabolism. This may not be necessary in children aged < 2 years. See text and footnote.^a

Aged < 1 Month (Investigational dose not Food and Drug Administration approved):

- 34–37 weeks gestational age (no lead in; please see text and footnote^a): 4 mg/kg/dose twice daily for the first week increasing to 6 mg/kg/dose twice daily thereafter
- ≥ 37 weeks gestational age to < 1 month: 6 mg/kg/dose twice daily (no lead in; please see text and footnote^a)
- See [Dosing: Special Considerations: Neonates \$\leq 14\$ Days and Premature Infants](#)

Aged ≥ 1 Month to < 8 Years:

- 200 mg/m² of body surface area (BSA)/dose twice daily after lead-in dosing.^a In children aged ≤ 2 years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

Aged ≥ 8 Years:

- 120–150 mg/m² BSA/dose twice daily after lead-in dosing^a (maximum dose of immediate-release tablets is 200 mg twice daily.)
- When adjusting the dose for a growing child,

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- 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 [Major Toxicities](#) section).
- 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 dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see [Dosing Considerations: Lead-In Requirement](#)).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see [Major Toxicities](#)).

Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine

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-m² dosage as the child grows, as long as there are no untoward effects.

| BSA Range (m ²) | NVP XR (mg) |
|-----------------------------|--------------------------------|
| 0.58–0.83 | 200 mg once daily (2 x 100 mg) |
| 0.84–1.16 | 300 mg once daily (3 x 100 mg) |
| ≥1.17 | 400 mg once daily (1 x 400 mg) |

Key to Abbreviations: BSA = body surface area; NVPXR = nevirapine extended release

Pediatric Dose Extended-Release Formulation (≥6 Years):

- Patients ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing. **Please see footnote.^a**

Adolescent and Adult Dose:

- 200 mg twice daily or 400 mg extended release once daily.

Nevirapine in Combination with Lopinavir/Ritonavir:

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

(glucuronidated metabolites).

- Dosing of nevirapine in patients with renal failure receiving hemodialysis: An additional dose of nevirapine should be given following dialysis.
- Dosing of nevirapine in patients with hepatic impairment: Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

^a Nevirapine is **usually** initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. 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 ≤2 years, some experts initiate nevirapine without a lead-in (see [Dosing Considerations: Lead-In Requirement](#) and [Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants](#)). In patients 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.

Rilpivirine (RPV, Edurant) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

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 ≥ 35 kg, see the Pharmacokinetics section below.

Adolescent (Weighing ≥ 35 kg) and Adult Dose:

Antiretroviral-Naive Patients with HIV RNA $\leq 100,000$ copies/mL or Virologically-Suppressed (HIV RNA <50 copies/mL) Patients with No History of Virologic Failure or Resistance to Rilpivirine and Other Antiretroviral (ARV) Drugs and Currently on Their First or Second Regimen:

- 25 mg once daily

Combination Tablet

[Complera] Emtricitabine plus Rilpivirine plus TDF Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- 1 tablet once daily in treatment-naive patients with baseline viral load <100,000 copies/mL or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Complera, and currently on their first or second regimen.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

Adolescent (Weighing ≥ 35 kg) and Adult Dose:

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than

Selected Adverse Events

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

Special Instructions

- 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 either at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug with a known risk of *Torsades de Pointes* (see <https://www.crediblemeds.org/>).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients

or equal to 100,000 copies per mL; or to replace a stable ART regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Odefsey.

with mild or moderate hepatic impairment.

- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.
- When using Complera see the [tenofovir disoproxil fumarate section](#); when using Odefsey see the [tenofovir alafenamide section](#).

Atazanavir (ATV, Reyataz) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

- [Evotaz] Atazanavir 300 mg plus cobicistat 150 mg

Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates and infants younger than 3 months. Atazanavir should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric Dose

Powder Formulation:^a

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

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

Atazanavir Powder^a

| Weight (kg) | Once-Daily Dose |
|---------------------------|--|
| 5 to <15 kg | Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food |
| 15 to <25 kg ^b | Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food |

Capsule Formulation:^a

- Not approved for use in children <6 years or <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 such as applesauce or 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 (<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 dosage of oral powder within 1 hour of preparation.
 - Because atazanavir can prolong the ECG

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

Atazanavir Capsules^a

| Weight (kg) | Once-Daily Dose |
|---------------------------|---|
| <15 kg | Capsules not recommended |
| 15 to <20 kg | Atazanavir 150 mg plus ritonavir ^c 100 mg, both once daily with food |
| 20 to <40 kg ^d | Atazanavir 200 mg plus ritonavir ^c 100 mg, both once daily with food |
| ≥40 kg | Atazanavir 300 mg plus ritonavir ^c 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-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

Antiretroviral-Naive Patients:

- Atazanavir 300 mg plus ritonavir 100 mg once daily with food.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 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](#)]).

Antiretroviral-Experienced Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg,

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 Drug Interactions using 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 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 (PPIs) 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 PPIs 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).
- Dosing of atazanavir in patients with hepatic impairment: Atazanavir should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. Atazanavir should not be used in patients with severe hepatic impairment.
- Dosing of atazanavir in patients with renal

both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.

impairment: No dose adjustment is required for patients with renal impairment. However, atazanavir should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

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.^e
- 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.^e
- Atazanavir 300 mg plus cobicistat^f 150 mg plus TDF 300 mg, all once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.
- Only boosted atazanavir should be used in combination with TDF because TDF decreases atazanavir exposure.

^a mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability is higher for the capsules than for the powder when studied in adults.

^b For a child who cannot swallow atazanavir capsules and who weighs ≥ 25 kg, 300 mg (6 packets) atazanavir powder plus ritonavir oral solution 100 mg, both once daily with food, may be used.

^c Either ritonavir capsules or ritonavir oral solution can be used.

^d Some experts would increase atazanavir to 300 mg at ≥ 35 kg to avoid under-dosing, especially when administered with TDF (see text for discussion).

^e For adult patients who cannot swallow capsules, atazanavir oral powder is taken once daily with food at the same adult dosage as the capsules along with ritonavir.

^f See Cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

Darunavir (DRV, Prezista) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Oral suspension: 100 mg/mL

Tablets [Prezista]: 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 (boosting agent): ritonavir (children and adults) or cobicistat (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 ≤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 ≥3 years:

- See table below for children aged ≥3 years who are antiretroviral **treatment-naïve and treatment-experienced** with or without one or more darunavir resistance-associated mutations.

Aged 3 to <12 Years and Weighing ≥10 kg

| Weight (kg) | Dose (Twice daily with food) ^a |
|---------------------------|---|
| 10 to <11 kg ^b | Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL) |
| 11 to <12 kg ^b | Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL) ^c |
| 12 to <13 kg ^b | Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL) ^c |
| 13 to <14 kg ^b | Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL) ^c |
| 14 to <15 kg | Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL) ^c |
| 15 to <30 kg | Darunavir 375 mg (combination of tablets or 3.8 mL ^d) plus ritonavir 48 mg (0.6 mL ^d) |
| 30 to <40 kg | Darunavir 450 mg (combination of tablets or 4.6 mL ^d) plus ritonavir 100 mg (tablet or 1.25 mL ^b) |
| ≥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 one 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 depending on 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 ≥ 40 kg)^e 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^f 150 mg (tablet) or coformulated as Prezcoibix **once daily with food**

Adolescent (Weight ≥ 30 to <40 kg; Treatment-Experienced with at Least 1 Darunavir Resistance-Associated Mutation):

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

Adolescent (Weight ≥ 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.

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.

Dosing in Patients with Renal Impairment:

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

^a Once-daily dosing is Food and Drug Administration-approved but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend it for children (see text under Frequency of Administration).

^b Note that the dose in children weighing 10 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.

^c Ritonavir 80 g/mL oral solution

^d The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

^e Some Panel members recommend once daily darunavir 675 mg (combination of tablets) plus ritonavir 100 mg once daily for adolescents with body weight ≥ 30 to <40 kg, especially those ≥ 12 years of age.

^f See [cobicistat section](#) for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

Fosamprenavir (FPV, Lexiva) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 HIV-Infected Children (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants ≥ 4 weeks and for treatment-experienced infants ≥ 6 months; however, the Panel does not recommend use in infants younger than 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.

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

Aged ≥ 6 Months to 18 Years:

Twice-Daily Dosage Regimens by Weight for Pediatric Patients ≥ 6 Months Using Lexiva Oral Suspension with Ritonavir

| Weight | Dose Fosamprenavir Plus Ritonavir Both twice daily ^a 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 |
| ≥ 20 kg | fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose |

^a 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 or buffered formulations of didanosine should take fosamprenavir at least 1 hour before or after antacid or didanosine 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 P450 3A4 (CYP3A4) 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 ≥ 39 kg. Ritonavir tablets can be used in patients weighing ≥ 33 kg.

Adolescent and Adult (Aged >18 Years) Dose:

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

ARV-Naive Patients

Boosted with Ritonavir, Twice-Daily Regimen:

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

Boosted with Ritonavir, Once-Daily Regimen:

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

Protease Inhibitor (PI)-Experienced Patients:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.
- **Note:** Once-daily administration of fosamprenavir plus ritonavir is not recommended.

Fosamprenavir in Combination with Efavirenz (Adult):

- Only fosamprenavir boosted with ritonavir should be used in combination with efavirenz.

Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily plus efavirenz 600 mg once daily.

PI-Naive Patients Only, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 300 mg plus efavirenz 600 mg, all once daily.

- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

Indinavir (IDV, Crixivan) (Last updated April 27, 2017; last reviewed April 27, 2017)

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/m² 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

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 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).
- If co-administered with didanosine, give indinavir and didanosine ≥1 hour apart on an empty stomach.
- 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
- Dosing in patients with hepatic impairment: Decreased dosage should be used 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 April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Pediatric Oral Solution: 80 mg/20 mg LPV/r per mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

Film-Coated Tablets: 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

Dosing Recommendations

Neonatal Dose (<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 because of potential toxicities.

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

Infant Dose (14 Days–12 Months):

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per m² of body surface area twice daily (approximates 16 mg/4 mg lopinavir/ritonavir 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 m² dose).

Pediatric Dose (>12 Months to 18 Years):

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily (maximum dose 400 mg/100 mg lopinavir/ritonavir twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg lopinavir/ritonavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg lopinavir/ritonavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

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

- Lopinavir/ritonavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- Lopinavir/ritonavir tablets must be swallowed whole. Do not crush or split tablets.
- Lopinavir/ritonavir oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of lopinavir/ritonavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- Lopinavir/ritonavir oral solution can be kept at room temperature up to 77° F (25° C) if used within 2 months. If kept refrigerated (2° to 8° C or 36° to 46° F) lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.
- Use of lopinavir/ritonavir once daily is specifically contraindicated if three or more of

- 230 mg/57.5 mg lopinavir/ritonavir per m² of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients <15 kg, this dose approximates 12 mg/3 mg lopinavir/ritonavir per kg body weight given twice daily and for patients ≥15 kg to 40 kg, this dose approximates 10 mg/2.5 mg lopinavir/ritonavir per kg body weight given twice daily. This dose **should not be used** in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

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

| Dosing Target | Recommended Number of 100-mg/25-mg Lopinavir/Ritonavir Tablets Given Twice Daily | |
|-------------------------|--|---|
| | 300 mg/m ² /dose given twice daily | 230 mg/m ² /dose given twice daily |
| Body Weight (kg) | | |
| 15 to 20 kg | 2 | 2 |
| >20 to 25 kg | 3 | 2 |
| >25 to 30 kg | 3 | 3 |
| >30 to 35 kg | 4 ^a | 3 |
| >35 to 45 kg | 4 ^a | 4 ^a |
| >45 kg | 4 ^a or 5 ^b | 4 ^a |

^a Four of the 100 mg/25 mg lopinavir/ritonavir tablets can be substituted with 2 tablets each containing 200 mg/50 mg lopinavir/ritonavir in children capable of swallowing a larger tablet.

^b In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, for body weight >45 kg, the Food and Drug Administration (FDA)-approved adult dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing.

Adult Dose (>18 Years):

- 800 mg/200 mg lopinavir/ritonavir once daily, **or**
- 400 mg/100 mg lopinavir/ritonavir 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 Instructions for list).

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—because higher lopinavir trough concentrations may be required to suppress resistant virus.

Metabolism/Elimination

- Cytochrome P (CYP) 3A4 inhibitor and substrate.
- Dosing of lopinavir/ritonavir in patients with hepatic impairment: Lopinavir/ritonavir is primarily metabolized by the liver. Caution should be used 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 lopinavir/ritonavir, 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.

In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):

- 400 mg/100 mg lopinavir/ritonavir twice daily.

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

Note: These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased lopinavir/ritonavir dosing is required with concomitant administration of these drugs.

- Once-daily dosing should **not** be used.

Pediatric Dose (>12 Months to 18 Years):

- 300 mg/75 mg lopinavir/ritonavir per m² of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

Adult Dose (>18 Years):

- FDA-approved dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing. Once-daily dosing should **not** be used.

Lopinavir/Ritonavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:

- Saquinavir and maraviroc doses may need modification (see the Saquinavir and Maraviroc sections for more information).

Nelfinavir (NFV, Viracept) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Neonate/Infant Dose:

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

Pediatric Dose (Aged 2–13 Years):

- 45–55 mg/kg twice daily

Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily
- Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia

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, patients should 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

- CYP2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

Saquinavir (SQV, Invirase) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Capsules: 200 mg

Tablets: 500 mg

Dosing Recommendations

Neonate and Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

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

Investigational Doses in Treatment-Experienced Children:

- Saquinavir must be boosted with ritonavir.

Aged <2 Years:

- No dose has been determined.

Aged ≥2 Years (Conditional Dosing Based on Limited Data; See Text):

| Weight (kg) | Dose Saquinavir plus Ritonavir |
|--------------|--|
| 5 to <15 kg | Saquinavir 50 mg/kg plus ritonavir 3 mg/kg, both twice daily |
| 15 to <40 kg | Saquinavir 50 mg/kg plus ritonavir 2.5 mg/kg, both twice daily |
| ≥40 kg | Saquinavir 50 mg/kg plus ritonavir 100 mg, both twice daily |

Adolescent (Aged ≥16 years) and Adult Dose:

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

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Increased bleeding episodes in patients with hemophilia
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (*Torsades de Pointes*) have been reported.

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 and saquinavir is contraindicated in patients with a prolonged QT interval.

Metabolism/Elimination

- Cytochrome P (CYP) 450 3A4 and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: use with caution.

Tipranavir (TPV, APTIVUS) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 used with ritonavir boosting. The ritonavir boosting dose used for tipranavir is higher than that used for other protease inhibitors.

Pediatric Dose (Aged <2 Years):

- Not approved for use in children aged <2 years.

Pediatric Dose (Aged 2–18 Years):

Note: Not recommended for treatment-naïve patients

Body Surface Area Dosing:

- Tipranavir 375 mg/m² plus ritonavir 150 mg/m², both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

Weight-Based Dosing:

- Tipranavir 14 mg/kg plus ritonavir 6 mg/kg, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

Adult Dose:

Note: Not recommended for treatment-naïve patients

- Tipranavir 500 mg (two 250-mg capsules) plus ritonavir 200 mg, both twice daily

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 with food.
- Tipranavir oral solution contains 116 IU vitamin E/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 bottle is 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;
- Dosing in patients with renal impairment: No dose adjustment required
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

Enfuvirtide (T-20, Fuzeon) (Last updated April 27, 2017; last reviewed

April 27, 2017)

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 April 27, 2017; last reviewed April 27, 2017)

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

Formulations

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

Oral Solution: 20 mg/mL

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants.

Pediatric Dose:

- Approved for use by children aged ≥ 2 years and weighing ≥ 10 kg

Recommended Dosage in Antiretroviral Experienced Children Aged ≥ 2 Years and Weighing ≥ 10 kg: Tablets or Oral Suspension

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]):

| Weight Band | Twice-Daily Dosing | Liquid 20 mg/mL | Tablets |
|-----------------|--------------------|-----------------|-------------------|
| 10 kg to <20 kg | 50 mg | 2.5 mL | 2 25-mg |
| 20 kg to <30 kg | 75 mg | 4 mL | 1 75-mg |
| 30 kg to <40 kg | 100 mg | 5 mL | 1 25-mg & 1 75-mg |
| >40 kg | 150 mg | 7.5 mL | 1 150-mg |

When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers:

| Weight Band | Twice-Daily Dosing | Liquid 20 mg/mL | Tablets |
|-----------------|--------------------|-----------------|----------|
| 10 kg to <20 kg | Not recommended | | |
| 20 kg to <30 kg | Not recommended | | |
| 30 kg to <40 kg | 300 mg | 15 mL | 1 300-mg |
| >40 kg | 300 mg | 15 mL | 1 300-mg |

When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor):

Not recommended

Selected Adverse Events

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

Special Instructions

- Maraviroc is recommended for patients with only CCR5-tropic HIV-1. Conduct testing with HIV tropism assay (see [Antiretroviral Drug-Resistance Testing in Adult and Adolescent Antiretroviral Guidelines](#)) before using MVC to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Do not use if CXCR4 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
- Dosing of maraviroc in patients with hepatic impairment: Use caution when administering maraviroc to patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations may be increased in patients with hepatic impairment.
- Dosing of maraviroc in adults and adolescents with renal impairment: refer to the

Adult Dose

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

manufacturer's prescribing information.

- Data are insufficient to make dosing recommendations for use of maraviroc in children concomitantly receiving non-interacting medications and weighing less than 30 kg or in all children concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor.

Dolutegravir (DTG, Tivicay) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Tablet: 10 mg, 25 mg, and 50 mg

Fixed-Dose Combination Tablet:

- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

Dosing Recommendations

Neonate/Infant Dose:

- Not approved for use in neonates/infants

Children Weighing ≥ 30 to < 40 kg:

- Not Food and Drug Administration-approved for use in children weighing < 30 kg.
- A clinical trial in antiretroviral (ARV) treatment-experienced (but integrase strand inhibitor [INSTI]-naive children) weighing < 30 kg is underway (see text).

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

^a These doses are for children who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1/CYP3A inducers

Note: Dolutegravir 10-mg and 25-mg tablets may be available in the retail pharmacy. If not available, when ordering dolutegravir 10-mg or 25-mg tablets, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GSK distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

Selected Adverse Events

- Insomnia
- Headache
- 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**.¹
- The efficacy of 50-mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).

Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- 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

Children and Adolescents (Weighing ≥ 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 ^a | 50 mg twice daily |

^a Combinations that do not include metabolic inducers should be considered where possible.

Combination Tablet

[Triumeq] Abacavir plus Dolutegravir plus Lamivudine:

Adolescent (Weighing ≥ 40 kg) and Adult Dose:

- 1 tablet once daily
- For use in patients who are ARV treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers

serum creatinine, but does not affect glomerular filtration.

- 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, VITEKTA) (Last updated April 27, 2017; last reviewed April 27, 2017)

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:

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

Dosing Recommendations

Note: Elvitegravir is only available in fixed-dose combination tablets with the pharmacokinetic (PK) enhancer (boosting agent) cobicistat (i.e., *Stribild* or *Genvoya*).

Pediatric Dose (Weighing <35 kg):

- No data on appropriate dose of elvitegravir in *Stribild* in children weighing <35 kg.
- Studies ongoing for dosing of *Genvoya* in children aged 6 to <12 years weighing 25 to <35 kg.

Adolescent (Weighing >35 kg) and Adult Dose:

Genvoya (Any Sexual Maturity Rating; Tanner Stage):^a

- One tablet once daily

Stribild (SMR 4 or 5):^a

- One tablet once daily

Selected Adverse Events

- Diarrhea (elvitegravir)
- Stribild-associated adverse events: Nausea, diarrhea, fatigue, headache. TDF—renal insufficiency, decreased bone mineral density, flatulence; cobicistat—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 used in combination with 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 increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF is 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 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 PK enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to **TDF and TAF** sections 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.

^a Stribild and Genvoya are Food and Drug Administration-approved for use in antiretroviral (ARV) treatment-naive adults or to replace the current ARV regimen in adults who are 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 Stribild or Genvoya.

Raltegravir (RAL, Isentress) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Tablets: 400 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 5 mL of water for final concentration of 20 mg/mL.

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

Dosing Recommendations

Neonate Dose:

- Not approved for use in neonates.
- Investigational dose for neonates ≥ 37 weeks of gestation and weighing ≥ 2 kg under study in IMPAACT P1110:
 - Birth to age 7 days: 1.5 mg/kg once daily
 - Aged 8–28 days: 3 mg/kg twice daily
 - Aged ≥ 4 weeks: 6 mg/kg twice daily (see below for approved infant and pediatric dose)
- No dosing information is available for preterm or low birthweight infants.

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

Infant and Pediatric Dose:

Oral Suspension Dosing Table^a

Children Aged ≥ 4 Weeks and Weighing ≥ 3 kg to < 20 kg:

| Body Weight (kg) | Volume (Dose) of Suspension to be Administered |
|------------------|--|
| 3 to < 4 | 1 mL (20 mg) twice daily |
| 4 to < 6 | 1.5 mL (30 mg) twice daily |
| 6 to < 8 | 2 mL (40 mg) twice daily |
| 8 to < 11 | 3 mL (60 mg) twice daily |
| 11 to < 14 | 4 mL (80 mg) twice daily |
| 14 to < 20 | 5 mL (100 mg) twice daily |

^a 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 5 mL (100 mg) twice daily.

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.
- Avoid taking aluminum and/or magnesium containing antacids.
- Chewable tablets can be chewed, crushed (before administration), or 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 original package with desiccant to protect from moisture.
- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided with a kit that includes two mixing cups, two dosing syringes, and 60 foil packets. Detailed

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

Pediatric Dose for Chewable Tablets and Film-Coated Tablets:

Children Weighing ≥ 11 kg:

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

Chewable Tablet Dosing Table^a

Note: Maximum dose of chewable tablets is 300 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 ^b twice daily |
| 28 to <40 | 200 mg twice daily | 2 X 100 mg twice daily |
| ≥ 40 | 300 mg twice daily | 3 X 100 mg twice daily |

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

^b The 100-mg chewable tablet can be divided into equal halves.

Film-Coated Tablets

Child/Adolescent Weighing ≥ 25 kg and Adult Dose:

- 400-mg film-coated tablet twice daily

instructions are provided in the Instructions for Use document. Each foil, single-use packet contains 100 mg of raltegravir, which will be suspended in 5 mL of water for final concentration of 20 mg/mL. 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
- Dosing of raltegravir in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of raltegravir in patients with renal impairment: No dosage adjustment necessary.

Cobicistat (COBI, TYBOST) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 300 mg
- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide 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 in adolescents and adults as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and the integrase inhibitor elvitegravir. Cobicistat is **not** interchangeable with ritonavir. See dosing information for specific PIs and elvitegravir 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)
- Stribild
- Evotaz
- Prezcobix
- Some Panel members consider that these agents may be appropriate in select children aged <18 years and weighing ≥ 35 kg; an expert in pediatric HIV infection should be consulted.

Not FDA-Approved for Use in Children Aged <12 Years or Weighing <35 kg:

- Genvoya
- Panel members consider that it may be appropriate to use Genvoya in children aged <12 years and weighing ≥ 35 kg; an expert in pediatric HIV infection should be consulted.

Child/Adolescent and Weighing ≥ 35 kg

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

Adult (Aged ≥ 18 Years) Dose:

- Cobicistat must be administered as
 - The combination tablet Stribild or 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 combinations with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see [Table 13i](#)). 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

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-naïve or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya |
| 150 mg orally once daily | Atazanavir 300 mg (co-formulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs | Treatment-naïve or treatment-experienced |
| 150 mg orally once daily | Darunavir 800 mg (co-formulated as Prezcoibix or given as a separate drug) orally once daily plus other ARV drugs | Treatment-naïve or treatment-experienced with no darunavir-associated resistance mutations |

- Cobicistat inhibits renal tubular secretion of creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

Dosing of Cobicistat 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 April 27, 2017; last reviewed April 27, 2017)

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

Formulations

Oral Solution (Contains 43% Alcohol by Volume): 80 mg/mL

Tablets: 100 mg

Dosing Recommendations

Ritonavir as a Pharmacokinetic (PK) Enhancer:^a

- Ritonavir is used as a PK enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs.

^a Ritonavir has antiviral activity but is not used as an antiviral agent (see text).

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, Prezco**b**ix, 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.
- To Increase Tolerability of Ritonavir Oral Solution in Children:
 - Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
 - Before administration, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.

- After administration, give a child strong-tasting foods such as maple syrup or 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) 3A4 and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.
- Dosing of ritonavir in patients with hepatic impairment: Ritonavir is primarily metabolized by the liver. No dosage 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.