Formulary Drug Reviews

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Tablets

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Generic Name: Elvitegravir/cobicistat/
emtricitabine/tenofovir disoproxil
fumarate tablets

Proprietary Name: Stribild (Gilead Sciences)

Approval Rating: 1S

Therapeutic Class: Antiretroviral Combinations

Similar Drugs: None

Sound- or Look-

Alike Names: None

INDICATIONS

Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (df) is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve.¹ Single agent elvi-

tegravir has also recently been submitted for approval for use in the treatment of HIV-1 infection in treatment-experienced adults.²

Combination agents approved for the treatment of HIV-1 infection are summarized in **Table 1**.

CLINICAL PHARMACOLOGY

This combination formulation contains an integrase strand transfer inhibitor (elvitegravir), a pharmacokinetic enhancer or booster (cobicistat), and 2 nucleotide analogue HIV-1 reverse transcriptase inhibitors (emtricitabine and tenofovir df).¹

Elvitegravir is an integrase strand transfer inhibitor that selectively inhibits the strand-transfer step of the integration process of viral DNA into host chromosomal DNA. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection.^{1,4,5}

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Table 1. US Food and Drug Administration–approved combination agents for treatment of HIV-1 infection^{1,3}

	<i>Combivir</i> (GlaxoSmithKline, Generics)	<i>Epzicom</i> (GlaxoSmithKline)	<i>Kaletra</i> (Abbott)	<i>Stribild</i> (Gilead)	<i>Trizivir</i> (ViiV)	<i>Truvada</i> (Gilead)
<i>Components</i>						
Integrase inhibitor				Elvitegravir		
Nucleoside/Nucleotide reverse transcriptase inhibitor	Lamivudine/ Zidovudine	Abacavir/ Lamivudine		Emtricitabine/ Tenofovir disoproxil fumarate	Abacavir/ Lamivudine/ Zidovudine	Emtricitabine / Tenofovir disoproxil fumarate
Protease inhibitor			Lopinavir			
Pharmacokinetic booster			Ritonavir	Cobicistat		
<i>Indications</i>						
Treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve				X		
Treatment of HIV-1 infection alone or with other antiretroviral agents					X	
Treatment of HIV-1 infection in combination with other antiretroviral agents	X	X	X			X
Preexposure prophylaxis						X

Cobicistat is a selective cytochrome P450 (CYP-450) 3A4 inhibitor; by inhibiting CYP3A4, it increases the systemic level of CYP3A4 substrates such as elvitegravir.^{1,4,5}

Emtricitabine is a synthetic nucleoside analogue reverse transcriptase inhibitor.¹

Tenofovir df is a prodrug of tenofovir, a nucleotide analogue reverse transcriptase inhibitor.¹

PHARMACOKINETICS

After oral administration with food, peak levels were reached after 4 hours for elvitegravir, after 3 hours for cobicistat and emtricitabine, and after 2 hours for tenofovir. When elvitegravir/cobicistat/emtricitabine/tenofovir df is taken with food, the mean systemic exposures of elvitegravir and tenofovir df are increased; therefore, it should always be taken with food. Plasma protein binding of elvitegravir is 98% to 99%, cobicistat is 97% to 98%, emtricitabine is less than 4%, and tenofovir df is less than 0.7%.¹

The median terminal half-lives of elvitegravir and cobicistat are approximately 12.9 and 3.5 hours, respectively.¹ The tenofovir elimination half-life is approximately 17 hours, while that of emtricitabine is approximately 10 hours.³

Elvitegravir is primarily metabolized by CYP3A enzymes but also undergoes glucuronidation via uri-

dine diphosphate glucuronosyltransferase (UGT) 1A1 and UGT1A3 enzymes. Cobicistat is metabolized by CYP3A and, to a minor extent, by CYP2D6 enzymes. Emtricitabine and tenofovir df are not significantly metabolized.^{1,5}

Elvitegravir is predominantly eliminated in the feces (94.8%) and, to a lesser extent, in the urine (6.7%). Cobicistat is also predominantly eliminated in the feces (86.2%) and, to a lesser extent, in the urine (8.2%). Emtricitabine and tenofovir are primarily excreted in the urine by a combination of glomerular filtration and active tubular secretion.¹

COMPARATIVE EFFICACY

Indication: Combination Antiviral Treatment for HIV-1 Antiretroviral-Naïve Patients

Studies

Drug: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate vs Atazanavir plus Ritonavir plus Emtricitabine/Tenofovir Disoproxil Fumarate

Reference: DeJesus E, et al, 2012⁶

Study Design: Randomized, double-blind, double-dummy, multicenter, international, noninferiority study

Study Funding: Gilead Sciences

Patients: 715 patients at least 18 years of age (mean age, approximately 38 years) with HIV-1 and no

previous antiretroviral treatment, a baseline plasma HIV RNA concentration of at least 5,000 copies/mL (mean, 4.8 log₁₀ copies/mL), and an estimated glomerular filtration rate (GFR) of at least 70 mL/min; most patients were men (approximately 90%), approximately 75% were white, and approximately 17% were black.

Intervention: Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir df 300 mg once daily with food or atazanavir 300 mg, ritonavir 100 mg, and emtricitabine 200 mg/tenofovir df 300 mg once daily with food.

Results:

Primary Endpoint(s):

- HIV RNA concentration of less than 50 copies/mL at week 48 in the intent-to-treat population: 89.5% treated with elvitegravir/cobicistat/emtricitabine/tenofovir df and 86.8% treated with atazanavir plus ritonavir plus emtricitabine/tenofovir df (adjusted treatment difference, 3%; 95% confidence interval [CI], -1.9% to 7.8%); in the per-protocol population, viral response was achieved in 97.5% and 97.7% of patients, respectively (adjusted difference, -0.1%; 95% CI, -2.6 to 2.4).

Secondary Endpoint(s):

- Achievement and maintenance of viral suppression: 86.1% of patients taking elvitegravir/cobicistat/emtricitabine/tenofovir df achieved viral suppression compared with 84.8% of patients taking atazanavir plus ritonavir plus emtricitabine/tenofovir df.
- Pure virological failure (HIV RNA less than 50 copies/mL) at 48 weeks: 89.8% of patients taking elvitegravir/cobicistat/emtricitabine/tenofovir df compared with 89% of patients taking atazanavir plus ritonavir plus emtricitabine/tenofovir df.
- Change in HIV RNA: elvitegravir/cobicistat/emtricitabine/tenofovir df reported to be associated with a greater mean reduction from baseline (data not provided).
- Change in CD4 cell count at 48 weeks: mean increase of 207 cells per mcL on elvitegravir/cobicistat/emtricitabine/tenofovir df compared with 211 cells per mcL on atazanavir plus ritonavir plus emtricitabine/tenofovir df.

Other Endpoint(s): Diarrhea, nausea, upper respiratory tract infection, and headache were the most common treatment-related adverse events in both treatment groups.

Comments: Met the prespecified 12% margin for noninferiority. Subgroup analysis did not reveal any

differences in response between treatment groups based on age, gender, race, baseline HIV RNA concentration, baseline CD4 count, or adherence.

Limitations: Only 10% of the patient population were women, making it hard to generalize the results to that population. Study was a noninferiority study with surrogate markers used for its endpoints.

Drug: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate vs Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate

Reference: Sax PE, et al, 2012⁷

Study Design: Randomized, double-blind, double-dummy, multicenter study

Study Funding: Gilead Sciences

Patients: 707 patients at least 18 years of age (mean age, 38 years) with baseline plasma HIV-1 RNA concentrations of at least 5,000 copies/mL (mean, 4.8 log₁₀ copies/mL), no previous use of antiretroviral drugs, and an estimated creatinine clearance (CrCl) of at least 70 mL/min; a majority of participants were men (approximately 89%), approximately 63% were white, and approximately 28% were black.

Intervention: Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir df 300 mg once daily with food or efavirenz 600 mg/emtricitabine 200 mg/tenofovir df 300 mg once daily at bedtime on an empty stomach.

Results:

Primary Endpoint(s):

- HIV RNA concentration of less than 50 copies/mL at week 48 in the intent-to-treat population: 87.6% in the elvitegravir/cobicistat/emtricitabine/tenofovir df group versus 84.1% in the efavirenz/emtricitabine/tenofovir df group (difference, 3.6%; 95% CI, -1.6% to 8.8%); in the per-protocol population, viral response was achieved in 94.9% and 96%, respectively (difference, -1%; 95% CI, -4.4% to 2.4%).

Secondary Endpoint(s):

- Achievement and maintenance of viral suppression: 85.9% with elvitegravir/cobicistat/emtricitabine/tenofovir df compared with 83.2% with efavirenz/emtricitabine/tenofovir df.
- Change in HIV RNA concentration: data not provided.
- Change in CD4 cell count from baseline: 239 cells per mcL in the elvitegravir/cobicistat/emtricitabine/tenofovir df group compared with 206 cells per mcL in the efavirenz/emtricitabine/tenofovir df group ($P = .009$).

Other Endpoint(s):

- Median estimated GFR decreased more in the elvitegravir/cobicistat/emtricitabine/tenofovir df group compared with the efavirenz/emtricitabine/tenofovir df group (-14.3 mL/min vs -3 mL/min; $P < .001$) as a result of cobicistat-induced increases in serum creatinine. Nausea was more common in the elvitegravir/cobicistat/emtricitabine/tenofovir df group compared with the efavirenz/emtricitabine/tenofovir df group (21% vs 14%; $P = .016$). Dizziness (24% vs 7%; $P < .001$), abnormal dreams (27% vs 15%; $P < .001$), insomnia (14% vs 9%; $P = .031$), and rash (12% vs 6%; $P = .009$) were more common in the efavirenz/emtricitabine/tenofovir df group.

Comments: Met the prespecified 12% margin for noninferiority. Subgroup analysis did not reveal differences in response between treatment groups based on gender, race, baseline HIV RNA concentration, baseline CD4 count, or adherence; results in patients 40 years and older favored elvitegravir/cobicistat/emtricitabine/tenofovir df.

Limitations: The number of women enrolled in the study was small, making it hard to generalize the findings to that population. Study was a noninferiority study with surrogate markers used for the endpoints.

Reference: Cohen C, et al, 2011⁴

Study Design: Randomized, double-blind, double-dummy, active control, multicenter study

Study Funding: Gilead Sciences

Patients: 71 patients at least 18 years of age (mean age, approximately 36 years) with at least 5,000 copies/mL of HIV-1 RNA in plasma and a CD4 cell count more than 50 cells/mL, an estimated CrCl of at least 80 mL/min, and no prior use of anti-HIV drugs; the majority of participants were men (approximately 92%), approximately 72% were white, and 24% were black; mean HIV-1 RNA level at baseline was approximately 4.59 log₁₀ copies/mL; median CD4 cell count was 354 and 436 cells/mL, respectively.

Intervention: Elvitegravir/cobicistat/emtricitabine/tenofovir df administered once daily with food or efavirenz/emtricitabine/tenofovir df at bedtime.

Results:

Primary Endpoint(s):

- Viral suppression defined as HIV-1 RNA less than 50 copies/mL at week 24: 90% in the elvitegravir/cobicistat/emtricitabine/tenofovir df group compared with 83% in the efavirenz/emtricitabine/tenofovir df group.

Secondary Endpoint(s):

- Safety and tolerability of regimens at week 48: 46% of patients taking elvitegravir/cobicistat/emtricitabine/tenofovir df experienced drug-related adverse events compared with 57% of patients taking efavirenz/emtricitabine/tenofovir df. None of the patients in the elvitegravir/cobicistat/emtricitabine/tenofovir df group discontinued use of therapy for an adverse event, but 1 patient in the efavirenz/emtricitabine/tenofovir df group discontinued use due to an adverse event related to the drug.
- Viral suppression through week 48: 90% in the elvitegravir/cobicistat/emtricitabine/tenofovir df group compared with 83% in the efavirenz/emtricitabine/tenofovir df group.

Comments: Patients in the efavirenz/emtricitabine/tenofovir df group tended to experience more drug-related nervous system and psychiatric disorder adverse events (26% and 43%, respectively) compared with the elvitegravir/cobicistat/emtricitabine/tenofovir df group, who experienced a 10% incidence of drug-related nervous system adverse events and a 17% incidence of psychiatric disorder adverse events.

Limitations: This was an early phase study that was not powered for a comparison of the efficacy of the 2 treatment regimens. Only 8% of participants were women.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Elvitegravir/cobicistat/emtricitabine/tenofovir df is contraindicated with the coadministration of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, as well as drugs that may reduce efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir df.¹ Table 2 lists drugs that are contraindicated with elvitegravir/cobicistat/emtricitabine/tenofovir df.

Warnings and Precautions

The use of nucleoside analogues, including tenofovir df, in combination with other antiretrovirals has led to reports of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases. Therefore, particular caution should be exercised when administering nucleoside analogues to any patient with known risk factors for liver disease. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or

Table 2. Drugs that are contraindicated with elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate¹

Drug	Reason
Alfuzosin	Increased alfuzosin concentrations
Cisapride	Increased cisapride concentrations
Dihydroergotamine	Increased ergot concentrations
Ergotamine	Increased ergot concentrations
Lovastatin	Increased lovastatin concentrations
Methylergonovine	Increased ergot concentrations
Midazolam, oral	Increased midazolam concentrations
Pimozide	Increased pimozide concentrations
Sildenafil, at dose for pulmonary arterial hypertension	Increased sildenafil concentrations
Simvastatin	Increased simvastatin concentrations
Triazolam	Increased triazolam concentrations
Rifampin	Decreased elvitegravir/cobicistat concentrations
St. John's wort	Decreased elvitegravir/cobicistat concentrations

pronounced hepatotoxicity. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors.¹

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with hepatitis B virus (HBV) and HIV-1 and have discontinued emtricitabine or tenofovir df. Patients who are coinfecting with HBV and HIV-1 should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment with elvitegravir/cobicistat/emtricitabine/tenofovir df.¹

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of elvitegravir/cobicistat/emtricitabine/tenofovir df. Urine glucose, estimated CrCl, and urine protein should be assessed prior to initiating therapy and routinely during therapy in all patients. Serum phosphorus should be monitored in patients who are at risk for renal impairment. Elvitegravir/cobicistat/emtricitabine/tenofovir df should not be initiated in patients with estimated CrCl less than 70 mL/min and should be avoided with concurrent or recent use of nephrotoxic agents. Elvitegravir/cobicistat/emtricitabine/tenofovir df should be discontinued if estimated CrCl declines less than 50 mL/min.¹

Elvitegravir/cobicistat/emtricitabine/tenofovir df is indicated for use as a complete regimen to treat HIV-1 and should not be coadministered with other antiretroviral products.¹

Tenofovir df has been associated with decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting

increased bone turnover. Assessment of BMD should be considered in patients who have a history of pathologic bone fracture or other risk factors of osteoporosis or bone loss.¹

Immune reconstitution syndrome has been reported in patients treated with elvitegravir/cobicistat/emtricitabine/tenofovir df. Autoimmune disorders such as Graves disease, polymyositis, and Guillain-Barré syndrome have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.¹

Patients receiving antiretroviral therapy have experienced redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance.¹

Elvitegravir/cobicistat/emtricitabine/tenofovir df is considered to be Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. Elvitegravir/cobicistat/emtricitabine/tenofovir df should only be used during pregnancy if the potential benefits outweigh the risks.¹

Breast-feeding while on elvitegravir/cobicistat/emtricitabine/tenofovir df should be avoided because of the potential for HIV transmission and the potential for serious adverse reactions in breast-feeding infants.¹

The safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir df has not been established in pediatric patients younger than 18 years.¹

The clinical studies of elvitegravir/cobicistat/emtricitabine/tenofovir df did not include enough

Table 3. Adverse effects and laboratory abnormalities reported in $\geq 5\%$ of patients treated with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, efavirenz/emtricitabine/tenofovir disoproxil fumarate, or atazanavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate¹

Adverse reactions	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (n = 701)	Efavirenz/emtricitabine/tenofovir disoproxil fumarate (n = 352)	Atazanavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate (n = 355)
Proteinuria	39%	29%	24%
Nausea	16%	9%	13%
Diarrhea	12%	11%	16%
Abnormal dreams	9%	26%	3%
Headache	7%	4%	6%
Elevated creatine kinase	5%	11%	7%
Fatigue	5%	7%	6%
Dizziness	3%	20%	4%
Rash	3%	15%	6%
Insomnia	3%	8%	1%
Flatulence	2%	< 1%	7%
Somnolence	1%	7%	1%
Ocular icterus	< 1%	0%	13%
Jaundice	0%	< 1%	8%

patients 65 years and older to determine whether they respond differently from younger patients. Therefore, caution should be used when considering use of this combination in patients older than 65 years, keeping in mind the frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.¹

Dose adjustment is not required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Because of a lack of pharmacokinetic or safety data in patients with severe hepatic impairment (Child-Pugh class C), the use of elvitegravir/cobicistat/emtricitabine/tenofovir df is not recommended.¹

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 5%) include nausea, diarrhea, abnormal dreams, headache, and fatigue.¹ Table 3 lists adverse effects occurring in at least 5% of patients in any treatment arm from the elvitegravir/cobicistat/emtricitabine/tenofovir df pivotal trials.

DRUG INTERACTIONS

Elvitegravir/cobicistat/emtricitabine/tenofovir df should not be administered with other antiretroviral medications for the treatment of HIV-1 infection.

Protease inhibitors or nonnucleoside reverse transcriptase inhibitors should not be used while taking elvitegravir/cobicistat/emtricitabine/tenofovir df because of the potential for drug-drug interactions, including altered and/or suboptimal pharmacokinetics of cobicistat, elvitegravir, or the concomitant anti-retroviral agent. Coadministration of elvitegravir/cobicistat/emtricitabine/tenofovir df with drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-glycoprotein, breast cancer-resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), or OATP1B3 may result in increased plasma concentrations of such drugs due to cobicistat's ability to inhibit these transporters. Elvitegravir is a modest inducer of CYP2C9 and may decrease the plasma concentrations of CYP2C9 substrates.¹ Table 4 summarizes potential drug interactions with elvitegravir/cobicistat/emtricitabine/tenofovir df.

Drugs that induce CYP3A4 activity are expected to decrease efficacy of elvitegravir and cobicistat by increasing their clearance. On the other hand, drugs that inhibit CYP3A may increase the plasma concentration of cobicistat.¹

Emtricitabine and tenofovir df are primarily excreted by the kidneys; therefore, coadministration with drugs that reduce renal function or compete for active

Table 4. Established and other potentially significant drug interactions reported in the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate product labeling¹

Concomitant drug class (drug name)	Effect on concentration	Recommendations
Antacids (eg, aluminum and magnesium hydroxide)	Decreases elvitegravir	Separate administration by 2 hours
Antiarrhythmics (amiodarone, bepridil, digoxin, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, quinidine)	Increases antiarrhythmics; increases digoxin	Use with caution; monitor
Antibacterials (clarithromycin, telithromycin)	Increases clarithromycin; increases telithromycin; increases cobicistat	Reduce clarithromycin dose in patients with CrCl 50 to 60 mL/min
Anticoagulants (warfarin)	Effect on warfarin unknown	Monitor INR
Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)	Increases carbamazepine; decreases elvitegravir; decreases cobicistat	Consider alternative anticonvulsants
Anticonvulsants (clonazepam, ethosuximide)	Increases clonazepam; increases ethosuximide	Monitor
Antidepressants: SSRIs (paroxetine); tricyclic antidepressants (amitriptyline, desipramine, imipramine, nortriptyline, bupropion); trazodone	Increases SSRIs; increases tricyclic antidepressants; increases trazodone	Titrate antidepressant dose carefully
Antifungals (itraconazole, ketoconazole, voriconazole)	Increases elvitegravir; increases cobicistat; increases itraconazole; increases ketoconazole; increases voriconazole	Dosages of ketoconazole and itraconazole should not exceed 200 mg/day; careful risk/benefit assessment necessary to justify voriconazole use
Antigout (colchicine)	Increases colchicine	Avoid combination in patients with renal or hepatic impairment; consult labeling for dosage recommendations for other situations (eg, treatment of gout flares, prevention of gout flares, treatment of Mediterranean fever)
Antimycobacterials (rifabutin, rifapentine)	Decreases elvitegravir; decreases cobicistat	Concurrent use is NOT recommended
Beta-blockers (metoprolol, timolol)	Increases beta-blockers	Consider dose reductions; monitor
Calcium channel blockers (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil)	Increases calcium channel blockers	Use with caution; monitor
Corticosteroids, systemic (dexamethasone)	Decreases elvitegravir; decreases cobicistat	Consider alternative systemic corticosteroid
Corticosteroids, inhaled/nasal (fluticasone)	Increases fluticasone	Consider alternative inhaled/nasal corticosteroids
Endothelin receptor antagonists (bosentan)	Increases bosentan	Consult labeling for dose adjustments
HMG-CoA reductase inhibitors (atorvastatin)	Increases atorvastatin	Initiate atorvastatin with lowest starting dose and titrate carefully
Hormonal contraceptives (norgestimate/ethinyl estradiol)	Increases norgestimate; decreases ethinyl estradiol	Consider risks/benefits
Immunosuppressants (cyclosporine, sirolimus, tacrolimus)	Increases immunosuppressants	Monitor

(continued)

Table 4. Established and other potentially significant drug interactions reported in the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate product labeling¹ (CONT.)

Concomitant drug class (drug name)	Effect on concentration	Recommendations
Inhaled beta-agonist (salmeterol)	Increases salmeterol	Coadministration is NOT recommended
Neuroleptics (perphenazine, risperidone, thioridazine)	Increases neuroleptics	Consider reduced neuroleptic dose
Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)	Increases in phosphodiesterase type 5 inhibitors	Consult labeling for dose adjustments; concomitant use with sildenafil in pulmonary arterial hypertension is contraindicated
Sedatives/hypnotics (benzodiazepines [eg, midazolam, clorazepate, diazepam, estazolam, flurazepam], buspirone, zolpidem)	Increases sedatives/hypnotics	Monitor; reduce dose of parenteral midazolam; concomitant use with oral midazolam is contraindicated; dose of other sedatives/hypnotics may need to be decreased

Note: HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; INR = international normalized ratio; SSRIs = selective serotonin reuptake inhibitors.

tubular secretion may increase concentration of emtricitabine, tenofovir df, and other renally eliminated drugs.¹

RECOMMENDED MONITORING

Urine glucose, estimated CrCl, and urine protein should be assessed prior to initiating therapy and routinely during therapy in all patients. Serum phosphorus should be monitored in patients who are at risk for renal impairment.¹ Patients should be observed for development of lactic acidosis and severe hepatomegaly with steatosis, as well as for development of immune reconstitution syndrome. The assessment of BMD should be considered in patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss.¹

Patients coinfecting with HIV-1 and HBV should be monitored for acute exacerbations of HBV using clinical and laboratory follow-up for at least several months after stopping treatment with elvitegravir/cobicistat/emtricitabine/tenofovir df.¹

DOSING

The recommended dosage for elvitegravir/cobicistat/emtricitabine/tenofovir df is 1 tablet taken once daily with food.¹

Therapy with elvitegravir/cobicistat/emtricitabine/tenofovir df should not be initiated in patients with estimated CrCl less than 70 mL/min. If estimated CrCl declines to less than 50 mL/min, therapy with the combination should be discontinued because the necessary adjustments in the dosing interval are not

possible for the emtricitabine and tenofovir df components.¹

No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of a lack of pharmacokinetic and safety data, use is not recommended in patients with severe hepatic impairment.¹

PRODUCT AVAILABILITY

Elvitegravir/cobicistat/emtricitabine/tenofovir df received US Food and Drug Administration approval on August 27, 2012.⁸ It is available as a combination tablet containing elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir df 300 mg supplied in bottles of 30 tablets. It should be stored at controlled room temperature (25°C [77°F]), with excursions permitted to 15° to 30°C (59° to 86°F), and dispensed in the original container.¹

DRUG SAFETY/RISK EVALUATION MITIGATION STRATEGY (REMS)

No REMS was required for elvitegravir/cobicistat/emtricitabine/tenofovir df approval.^{1,8}

CONCLUSION

Elvitegravir/cobicistat/emtricitabine/tenofovir df offers a single-tablet, once-daily regimen for the treatment of HIV-1 infection in patients not previously treated with antiretroviral therapy. Rates of viral response were comparable to other regimens and the combination was well tolerated. It has the advantage over some HIV-1 drug regimens of a decreased pill burden, combined with once-daily dosing.

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