PDL DRUG REVIEW

Proprietary Name: Odefsey®
Common Name: emtricitabine, rilpivirine HCl, & tenofovir alafenamide fumarate
PDL Category: Antiretrovirals

Comparable Products	Preferred Drug List Status
Atripla	Recommended
Complera	Non-Preferred

Summary

Pharmacology/Usage: Odefsey® is a fixed-dose combination tablet containing emtricitabine (a synthetic nucleoside analog reverse transcriptase inhibitor, HIV-1 NRTI), rilpivirine (an HIV-1 non-nucleoside reverse transcriptase inhibitor; NNRTI), and tenofovir alafenamide (TAF). TAF is a prodrug of tenofovir, an acyclic nucleoside phosphonate [nucleotide] analog of adenosine 5'-monophosphate. TAF is phosphorylated to the active metabolite tenofovir diphosphate, which inhibits HIV-1 replication through incorporation into viral DNA by the HIV reverse transcriptase and results in DNA chain termination.

Indications: As a complete regimen for the treatment of HIV-1 infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA ≤100,000 copies per ml; OR to replace a stable antiretroviral 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®.

There is no pregnancy category with this product; however, the risk summary indicates that there are insufficient human data on the use during pregnancy to inform any drug-associated risk of birth defects and miscarriage. Tenofovir alafenamide (TAF) and rilpivirine have not been evaluated in women during pregnancy, but emtricitabine use during pregnancy has been evaluated in a limited number of women. Available data does not show a difference in the risk of overall major birth defects for emtricitabine (2.4%) as compared with the background rate for major birth defects in a US reference population of the Metropolitan Atlanta Congenital Defects Program (2.7%). The safety and efficacy of use as a complete regimen for the treatment of HIV-1 infection in children less than 12 years of age have not been established.

Dosage Forms: Capsule-shaped, film-coated Tablets: 200mg emtricitabine, 25mg rilpivirine (equivalent to 27.5mg rilpivirine HCl), and 25mg tenofovir alafenamide (TAF; equivalent to 28mg tenofovir alafenamide fumarate)

Recommended Dosage: Prior to starting Odefsey®, patients should be tested for hepatitis B virus infection. In addition, estimated CrCl, urine glucose, and urine protein should be assessed before starting treatment and monitored during treatment. In virologically-suppressed patients, it is recommended to have monitoring of HIV-1 RNA and regimen tolerability to assess for potential virologic failure or rebound after starting Odefsey®.

Take one tablet once daily with a meal in the following populations: adults/pediatric patient's ≥12 years of age with body weight ≥35kg and a CrCl ≥30ml/min.

Dose adjustments are not required in patients with mild or moderate hepatic impairment; however, use has not been studies in patients with severe hepatic impairment. While dose adjustments are not required in patients with estimated CrCL ≥30ml/min, the use of Odefsey® is not recommended in patients with severe renal impairment (estimated CrCl <30ml/min).

Drug Interactions: Rilpivirine is mainly metabolized by CYP3A, and thus concomitant use with drugs that inhibit or induce CYP3A may affect the clearance of rilpivirine. Please refer to the contraindications section for further drug-interactions. It is recommended to consider alternative medications to Odefsey® in patients taking a drug with a known risk of Torsades de Pointes. As emtricitabine and tenofovir are mainly excreted by the kidneys, the concomitant use of Odefsey® with drugs that reduce renal function or compete for active tubular secretion may increase levels of these drugs and thus increase the risk of adverse reactions. The concomitant use with rifabutin is not recommended. It is recommended to administer antacids at least 2 hours before or at least 4 hours after Odefsey®. It is recommended to give H2 receptor antagonists at least 12 hours before or at least 4 hours after Odefsey®. When possible, it is recommended to use alternatives to macrolide/ketolide antibiotics (e.g. clarithromycin, erythromycin, telithromycin), such as azithromycin, with Odefsey®. While dose adjustments are not required if using Odefsey® concomitantly with methadone, it is recommended to clinically monitor the combination. Again, while dose adjustments are not required, it is recommended to clinically monitor for breakthrough fungal infections if azole antifungals are used concomitantly with Odefsey®.

Common Adverse Drug Reactions: *There was no placebo data to compare with this product.* In pooled clinical trials of HIV-1 infected adults, the most frequently reported adverse reactions in patients treated with rilpivirine plus emtricitabine/tenofovir disoproxil fumarate (TDF) included headache, depressive disorders, and insomnia. The most common adverse reactions that led to discontinuation in this treatment group were psychiatric disorders and rash.

Odefsey® has a box warning regarding the risk of lactic acidosis/severe hepatomegaly with steatosis, as well as post treatment acute exacerbation of hepatitis B. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs in combination with other antiretrovirals. The warning adds that Odefsey® is not approved for the treatment of chronic hepatitis B virus and the safety and efficacy of use have not been established in patients co-infected with HIV-1 and hepatitis B. Severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV-1 and hepatitis B virus and have discontinued products containing emtricitabine and/or tenofovir disoproxil fumarate (TDF). Last, the warning adds that hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are co-infected with HIV-1 and hepatitis B and discontinue Odefsey®.

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. Autoimmune disorders have also been reported to occur in the setting of immune reconstitution.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs. Nevertheless, in clinical trials with emtricitabine plus TAF with elvitegravir plus cobicistat, there were no cases of Fanconi syndrome or proximal renal tubulopathy. In clinical trials with this drug combination that included patients with eGRF >50ml/min, serious renal adverse events or discontinuations due to renal disease were reported in <1% of patients. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including NSAIDs, are increased risk of developing renal-related adverse reactions. Odefsey® is not recommended in patients with estimated CrCl <30ml/min as data in this population are not sufficient.

In clinical trials, TAF and tenofovir have been associated with decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism that suggest increased bone turnover. In clinical trials, a significant decline in BMD was seen in 15% of patients treated with emtricitabine plus TAF with elvitegravir plus cobicistat. It is recommended to assess BMD for adults and pediatric patients treated with Odefsey® who have a

history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. In addition, calcium and vitamin D supplementation may be beneficial for this patient population.

There have also been cases of osteomalacia associated with proximal renal tubulopathy with the use of TDF-containing products. While not seen in clinical trials of emtricitabine plus TAF with elvitegravir plus cobicistat, the risk of osteomalacia with Odefsey® is not known.

Contraindications: Administration with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the antimycobacterials rifampin and rifapentine; proton pump inhibitors such as dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole; systemic dexamethasone (more than a single dose); and St. John's wort.

Manufacturer: Gilead Sciences

Analysis: The efficacy of emtricitabine, rilpivirine, and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults was established in trials of emtricitabine plus rilpivirine/tenofovir disoproxil fumarate (TDF) in HIV-1 infected adults as initial therapy with no antiretroviral treatment history (N=550) and to replace a 1^{st} or 2^{nd} stable antiretroviral regimen in those who were virologically-suppressed with no history of virologic failure or for ≥6 months with no known resistance substitutions (N=317). The virologic response in these two populations combined was 77% at week 96 and 89% at week 48, respectively. In treatment-naïve subjects, the virologic response rate at 96 weeks was 83% in patients with baseline HIV-1 RNA ≤100,000 copies/ml and 71% in patients with baseline HIV-1 RNA >100,000 copies/ml. The virologic response rate at 96 weeks in those with baseline CD4+ cell counts <200 cells/mm^3 was 68% and with baseline CD4+ cell count ≥200 cells/mm was 82%.

The efficacy of emtricitabine, rilpivirine, and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in adults was also established in trials of emtricitabine plus TAF with elvitegravir plus cobicistat when used as initial therapy with no antiretroviral treatment history (N=866) and to replace a stable antiretroviral regimen in those who were virologically-suppressed for ≥6 months with no known resistance substitutions (N=799). Results suggested that at week 48, 92% and 96% of the two populations, respectively, had HIV-1 RNA <50 copies/ml.

The efficacy of emtricitabine, rilpivirine, and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in the pediatric population was also established in trials with emtricitabine plus TAF with elvitegravir plus cobicistat in 23 patients aged 12 to less than 18 years of age weighing ≥35kg. The virologic response rate was 91% at 24 weeks.

The efficacy of emtricitabine, rilpivirine, and tenofovir alafenamide (TAF) for the treatment of HIV-1 infection in the pediatric population was also established in trials with rilpivirine in combination with other antiretroviral agents. The majority of subjects (N=24/36) received rilpivirine in combination with emtricitabine and TDF. Of these 24, only 20 had a baseline HIV-1 RNA ≤100,000 copies/ml. The virologic response rate in these 20 subjects was 80% at 48 weeks.

In a trail with emtricitabine plus TAF with elvitegravir plus cobicistat that included HIV-1 infected adult patients with estimated CrCl >30ml/min but <70ml/min (N=248), 95% of this population had HIV-1 RNA <50 copies/ml at week 24.

Place in Therapy: Odefsey® is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patient's ≥12 years of age as initial therapy in those who have no antiretroviral treatment history with HIV-1 RNA ≤100,000 copies/ml or to replace a stable antiretroviral 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®. While Odefsey® use is not recommended in patients with estimated creatinine clearance <30ml/min, dose adjustments are not required in patients with estimated creatinine clearance ≥30ml/min. Complera®, a combination regimen that contains the same active ingredients of Odefsey® except contains tenofovir disoproxil fumarate rather than TAF, should not be

initiated in patients with moderate, severe, or end-stage renal impairment with an estimated creatinine clearance <50ml/min or that require dialysis.[2]

There is evidence to suggest that TAF component of Odsfsey® is less likely to cause renal tubulopathy than similar formulations that contain tenofovir disoproxil fumarate. There is also evidence suggesting that patients on TAF formulations may have less bone loss than those on TDF formulations. Efficacy appears to be similar between the two formulations. However, Odefsey is not cost effective when compared with other low pill burden regimens containing the same or similar ingredients. It is recommended that Odefsey® be made non-preferred and require prior authorization for those few whose treatment needs cannot be met with other more cost effective low pill burden regimens.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Odefsey [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016.

[2] Complera [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016

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