Pharmaceutical Approval Update
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Emtricitabine/Rilpivirine/Tenofovir Alafenamide (Odefsey)

**Manufacturer:** Gilead Sciences, Foster City, California  
**Date of Approval:** March 1, 2016

**Indication:** Odefsey is indicated as a treatment for human immunodeficiency virus-1 (HIV-1) infection in patients 12 years of age and older as initial therapy in those with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) for at least six months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey. 

**Drug Class:** Odefsey is a three-drug combination of emtricitabine and tenofovir alafenamide (TAF, a prodrug of tenofovir), both HIV nucleoside analogue reverse transcriptase inhibitors, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor. Emtricitabine and TAF are from Gilead Sciences, and rilpivirine is from Janssen Sciences Ireland.

**Uniqueness of Drug:** Odefsey is the smallest pill of any single-tablet regimen for the treatment of HIV infection.

**Warnings and Precautions:**

**Lactic acidosis/severe hepatomegaly with steatosis.** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues in combination with other antiretrovirals. Most of these cases occurred in women. Odefsey should be discontinued in patients who develop clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

**Severe acute exacerbation of hepatitis B in patients coinfected with HIV-1 and hepatitis B virus (HBV).** Patients with HIV-1 infection should be tested for the presence of HBV before initiating antiretroviral therapy. Odefsey is not approved for the treatment of chronic HBV infection, and the safety and efficacy of Odefsey have not been established in patients coinfected with HIV-1 and HBV.

**Skin and hypersensitivity reactions.** Severe skin and hypersensitivity reactions have been reported with rilpivirine-containing regimens. Odefsey should be discontinued immediately if signs or symptoms of severe skin or hypersensitivity reactions develop.

**Loss of virological response due to drug interactions.** The concomitant use of Odefsey and other drugs may result in known or potentially significant drug interactions, some of which may lead to the loss of the therapeutic effect of Odefsey and possible development of resistance due to reduced exposure of rilpivirine.

**Prolongation of QTc interval with higher than recommended doses.** In healthy subjects, higher than recommended doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval on electrocardiograms. Clinicians should consider alternatives to Odefsey when the treatment is to be coadministered with a drug with a known risk of torsade de pointes or when administered to patients at higher risk of torsades de pointes.

**Depressive disorders.** Depressive disorders have been reported with rilpivirine.

**Hepatotoxicity.** Hepatic adverse events have been reported in patients receiving a rilpivirine-containing regimen.

**Fat distribution.** Redistribution or accumulation of body fat has been observed in patients receiving antiretroviral therapy. A causal relationship has not been established.

**Immune reconstitution syndrome (IRS).** IRS has been reported in patients treated with combination antiretroviral therapy, including emtricitabine and rilpivirine, both components of Odefsey.

**New onset or worsening renal impairment.** Renal impairment, including cases of acute renal failure, has been reported with the use of tenofovir prodrugs in human clinical trials.

**Bone loss and mineralization defects.** In human trials, TAF and tenofovir have been associated with decreases in bone mineral density and with increases in biochemical markers of bone metabolism suggestive of increased bone turnover.

**Dosage and Administration:** Odefsey contains 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of TAF. The recommended dosage of Odefsey is one tablet taken once daily with a meal in adults and pediatric patients (12 years of age and older) with a body weight ≥ 35 kg or more and a creatinine clearance of ≥ 30 mL or more per minute.

**Commentary:** The FDA approval of Odefsey was supported by a bioequivalence study demonstrating that Odefsey achieved higher than recommended doses of rilpivirine and TAF in the blood similar to Genvoya (Gilead Sciences, 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) and drug levels of rilpivirine similar to Edurant (Johnson & Johnson/Janssen Products, rilpivirine 25 mg).

**Sources:** Gilead Sciences, Odefsey prescribing information

Dapsone Gel, 7.5% (Aczone)

**Manufacturer:** Allergan, Dublin, Ireland  
**Date of Approval:** February 25, 2016

**Indication:** Dapsone gel, 7.5%, is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

**Drug Class:** Dapsone is a sulfone, an organic sulfur compound.

**Uniqueness of Drug:** Dapsone gel, 7.5%, offers once-daily dosing and a new pump delivery system.

**Warnings and Precautions:**

**Hematological effects.** The use of dapsone gel, 7.5%, should be avoided in patients with congenital or idiopathic methemoglobinemia. Dapsone gel, 7.5%, should be discontinued if signs and symptoms suggestive of hemolytic anemia occur.

**Peripheral neuropathy.** Peripheral neuropathy has been reported with oral dapsone treatment.

**Skin reactions.** Skin reactions have been reported with oral dapsone treatment.

**Dosage and Administration:** Dapsone gel, 7.5%, is for topical use only. After the skin has been gently washed and patted dry, a pea-sized amount of the gel is applied in a thin
layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. If there is no improvement after 12 weeks, treatment with dapson gel, 7.5%, should be reassessed.

Commentary: The safety and efficacy of dapson gel, 7.5%, were assessed in two identically designed, 12-week, randomized, double-blind, vehicle-controlled studies. At week 12, inflammatory lesions were reduced by 15.8 lesions with dapson gel (54.6%) compared with 13.9 lesions with vehicle (48.1%), and noninflammatory lesions were reduced by 20.7 lesions (45.1%) compared with 18.0 lesions (39.4%), respectively. The Global Acne Assessment Score success rates were 29.8% and 21.1% for dapson gel and vehicle, respectively.

Sources: Allergan, Aczone gel, 7.5%, prescribing information

Tofacitinib, Extended Release (Xeljanz XR)
Manufacturer: Pfizer, New York, New York
Date of Approval: February 24, 2016
Indication: Extended-release tofacitinib is indicated for the treatment of adult patients with moderate-to-severe active rheumatoid arthritis (RA) who have had an inadequate response to or are intolerant of methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Drug Class: Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hemopoiesis and immune cell function.

Uniqueness of Drug: Xeljanz XR is the only once-daily oral JAK inhibitor available for the treatment of moderate-to-severe RA.

Warnings and Precautions:
Boxed warning. Patients treated with Xeljanz XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

Malignancy and lymphoproliferative disorders. Clinicians should consider the risks and benefits of Xeljanz XR before initiating therapy in patients with a known malignancy other than a successfully treated nonmelanoma skin cancer or when considering continuing Xeljanz XR in patients who develop a malignancy. Malignancies were observed in clinical studies of standard Xeljanz.

Laboratory abnormalities. Treatment with standard Xeljanz was associated with initial lymphocytosis after one month of exposure, followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Clinicians should avoid initiating Xeljanz XR in patients with a low lymphocyte count (less than 500 cells/mm³). Treatment with standard Xeljanz was also associated with an increased incidence of neutropenia (less than 2,000 cells/mm³) compared with placebo. Clinicians should avoid initiating Xeljanz XR in patients with an absolute neutrophil count of less than 1,000 cells/mm³. Neutrophil counts should be monitored at baseline; after four to eight weeks of treatment; and every three months thereafter.

Anemia: Clinicians should avoid initiating Xeljanz XR in patients with a low hemoglobin level (i.e., less than 9 g/dL).

Dosage and Administration: The recommended dosage of Xeljanz XR is 11 mg once daily. Patients treated with standard Xeljanz may be switched to Xeljanz XR the day after the last dose of Xeljanz. Xeljanz XR can be taken with or without methotrexate.

Commentary: It is not known whether Xeljanz XR is safe and effective in children or in people with hepatitis B or C. Xeljanz XR is not for people with severe liver problems.

Sources: Pfizer, Xeljanz/Xeljanz XR prescribing information

Brivaracetam (Briviact)
Manufacturer: UCB, Inc., Smyrna, Georgia
Date of Approval: February 19, 2016
Indication: Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

Drug Class: Brivaracetam, the 4-n-propyl analogue of levetiracetam, is a racemate derivative with anticonvulsant properties.

Uniqueness of Drug: Brivaracetam displays high selective affinity for synaptic vesicle protein 2A in the brain, which may account for its anticonvulsant effect.

Warnings and Precautions:
Suicidal behavior and ideation. Patients should be monitored for suicidal behavior and ideation.

Neurological adverse reactions. Patients should be monitored for somnolence and fatigue, and they should be advised not to drive or operate machinery until they have gained sufficient experience on brivaracetam.

Psychiatric adverse reactions. Behavioral reactions to brivaracetam include psychotic symptoms, irritability, depression, aggressive behavior, and anxiety. Patients should be monitored for these symptoms.

Hypersensitivity (bronchospasm and angioedema). Patients should be advised to seek immediate medical care if hypersensitivity reactions occur. Brivaracetam should be discontinued and not restarted in patients exhibiting hypersensitivity.

Withdrawal of antiepileptic drugs. Brivaracetam should be withdrawn gradually.

Dosage and Administration: Brivaracetam is available as a tablet for oral use, as an oral solution, and as an injection for intravenous use. The recommended starting dosage for brivaracetan is 50 mg twice daily (100 mg per day). Based on the individual patient’s tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day). Brivaracetan injection may be used when oral administration is temporarily not feasible.

Commentary: Brivaracetam must be dispensed with a medication guide for patients, which provides important information about the medication’s use and risks. As is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks. Rarely, patients may experience an allergic reaction associated with swelling of the lips, eyelids, or tongue with or without difficulty breathing.

Sources: FDA, Briviact prescribing information

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