Prasterone (Intrarosa) Vaginal Insert

Manufacturer: Endoceutics, Quebec, Canada
Date of Approval: November 16, 2016
Indication: Prasterone is indicated for the treatment of moderate-to-severe dyspareunia due to menopause.
Drug Class: Intravaginal steroid

Uniqueness of Drug: This is the first agent approved by the Food and Drug Administration (FDA) to treat women experiencing moderate-to-severe pain during sexual intercourse (dyspareunia), a symptom of vulvar and vaginal atrophy (VVA), due to menopause. During menopause, vaginal tissue estrogen levels decrease, which may lead to VVA that can cause symptoms such as pain during sexual intercourse. In addition, Intrarosa is the first FDA-approved product containing the active ingredient prasterone, which is also known as dehydroepiandrosterone (DHEA). Other forms of DHEA are used in dietary supplements that are not approved by the FDA.

Warnings and Precautions:
Current or past history of breast cancer. Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. Intrarosa has not been studied in women with a history of breast cancer.

Use in pregnant women and lactating women. Use of Intrarosa is limited to postmenopausal women. Animal reproduction studies have not been conducted with prasterone, and there are no data on use of this agent in pregnant women. In addition, there is no information on the presence of prasterone in human milk, the effects on the breastfed infant, or effects on milk production.

Contraindications. Intrarosa should not be used in any postmenopausal woman with undiagnosed abnormal genital bleeding. The cause of any persistent or recurring genital bleeding should be evaluated to determine the cause prior to being considered for treatment with Intrarosa.

Dosage and Administration: Intrarosa is available as a 6.5-mg vaginal insert. The dose is one insert, once daily at bedtime, using the provided applicator.

Commentary: The efficacy of once-daily, intravaginal Intrarosa was established in two 12-week placebo-controlled clinical trials of 406 healthy postmenopausal women (40–80 years of age), who identified moderate-to-severe pain during sexual intercourse as their most bothersome symptom of VVA. Women were randomly assigned to receive Intrarosa or a placebo vaginal insert. Intrarosa, when compared to placebo, was shown to reduce the severity of pain experienced during sexual intercourse. The safety of Intrarosa was established in four 12-week placebo-controlled trials and one 52-week open-label trial. The most common adverse reactions were vaginal discharge (14.2%) and abnormal Pap smear (2.1%). Among the patients with abnormal Pap smears, there was one case of low-grade squamous intraepithelial lesion and 10 cases of atypical cells of undetermined significance.

Sources: Endoceutics, Intrarosa prescribing information, FDA

Crisaborole (Eucrisa) Ointment, 2%
Manufacturer: Anacor Pharmaceuticals, Palo Alto, California
Date of Approval: December 14, 2016
Indication: Crisaborole ointment is indicated for the topical treatment of mild-to-moderate atopic dermatitis (AD) in patients 2 years of age and older.

Drug Class: Phosphodiesterase 4 (PDE-4) inhibitor

Uniqueness of Drug: Crisaborole ointment is the first and only nonsteroidal topical monotherapy that inhibits the PDE-4 enzyme in the skin. Overactive PDE-4 has been shown to contribute to the signs and symptoms of AD, also known as eczema. AD is a chronic condition impacting nearly 18 million children and adults in the United States. Of all people living with AD, approximately 90% have a mild-to-moderate form. Crisaborole is the first new prescription product to treat mild-to-moderate AD in more than 10 years.

Warnings and Precautions:
Hypersensitivity reactions. Contact urticaria and hypersensitivity reactions have occurred in crisaborole-treated patients. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, discontinue crisaborole immediately and initiate appropriate therapy.

Use in pregnant women. There are no crisaborole data available in pregnant women to inform of drug-associated risks for major birth defects and miscarriage. In animal reproduction studies, there were no adverse developmental effects observed with oral crisaborole in pregnant rabbits and rats during organogenesis at doses up to three and five times, respectively, of the maximum recommended human dose.

Use in lactating women. There is no information available on the presence of crisaborole in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production after topical application to women who are breastfeeding. Crisaborole ointment is systemically absorbed; therefore, risks and benefits should be weighed before recommending this agent to a breastfeeding woman.

Adverse reactions. The most common adverse reaction to crisaborole ointment in clinical trials was application-site pain, which occurred in 4% of patients (n = 45) compared with 1% (n = 6) of placebo-treated patients following twice-daily administration over four weeks of treatment.

Dosage and Administration: A thin layer of crisaborole ointment should be applied twice daily to affected areas.
Commentary: The safety and efficacy of crisaborole were established in two vehicle-controlled trials with a total of 1,522 participants ranging in age from 2 to 79 years with mild-to-moderate atopic dermatitis. Patients had a 5% to 95% treatable body surface area. Overall, participants receiving crisaborole ointment achieved greater response, with clear or almost clear skin after 28 days of treatment.

Sources: Anacor Pharmaceuticals, Euceris prescribing information

Tenovir Alafenamide (Vemlidy) Tablets
Manufacturer: Gilead Sciences, Inc., Foster City, California
Date of Approval: November 10, 2016
Indication: Tenovir alafenamide (TAF) tablets are indicated as a once-daily treatment for adults with chronic hepatitis B virus (HBV) infection with compensated liver disease.

Drug Class: HBV nucleoside reverse transcriptase inhibitor

Uniqueness of Drug: TAF is a novel, targeted prodrug of tenofovir that has demonstrated antiviral efficacy similar to and at a dose less than one-tenth that of the 300-mg tenofovir disoproxil fumarate (TDF) tablet (Viread, Gilead). TAF has greater plasma stability and can more efficiently deliver tenofovir to hepatocytes; therefore, it can be given at a lower dose, resulting in less circulating tenofovir. TAF, therefore, has improved renal and bone laboratory safety parameters compared with TDF.

Warnings and Precautions:

Boxed warning: lactic acidosis/severe hepatomegaly with steatosis. Lactic acidosis/severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including TAF, in combination with other antiretrovirals. Most cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. TAF should be used with caution in any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. TAF treatment should be withheld in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Boxed warning: post-treatment severe acute exacerbation of HBV. Discontinuation of anti-HBV therapy may lead to severe acute HBV exacerbations. Hepatic function should be closely monitored in patients who discontinue TAF. If appropriate, restarting of anti-HBV therapy may be warranted.

HBV and HIV-1 coinfected. TAF monotherapy is not recommended for treating human immunodeficiency virus type-1 (HIV-1) infection because resistance may develop.

New onset or worsening renal impairment. Renal impairment, including acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir prodrugs in both animal toxicity studies and human trials. In TAF clinical trials, no cases of Fanconi syndrome or proximal renal tubulopathy were reported. Patients taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), are at increased risk of developing renal-related adverse effects. Assessment of serum creatinine, serum phosphorus, estimated creatinine clearance, urine glucose, and urine protein is recommended before initiating TAF therapy and during therapy as clinically appropriate. TAF should be discontinued in patients who develop clinically significant renal function decreases or evidence of Fanconi syndrome.

Drug interactions. TAF is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma TAF concentrations, which may lead to loss of therapeutic effect. Coadministration of TAF with other drugs that inhibit P-gp and BCRP may increase TAF absorption and increase the TAF plasma concentration.

Because TAF is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs; this may increase the risk of adverse reactions. Some examples of these drugs include, but are not limited to, acyclovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides, and high-dose or multiple NSAIDs.

Other established or potentially clinically significant drug interactions are listed in the full prescribing information.

No significant drug interactions have been observed based on TAF drug interaction studies with etinyl estradiol, itraconazole, ketoconazole, ledipasvir/sofosbuvir, midazolam, norgestimate, sertraline, sofosbuvir, and sofosbuvir/velpatavir.

Dosage and Administration: The recommended TAF dose is 25 mg (one tablet) taken orally once daily with food. No dosage adjustment is required in patients with mild, moderate, or severe renal impairment or with mild hepatic impairment. TAF is not recommended in patients with end-stage renal disease (estimated creatinine clearance less than 15 mL per minute) or with decompensated (Child–Pugh B or C) hepatic impairment.

Commentary: The safety and efficacy of TAF is supported by 48-week data from two randomized phase 3 studies (Studies 108 and 110) in 1,298 treatment-naïve and treatment-experienced adults with chronic HBV infection. Study 108 randomized and treated 425 hepatitis B e antigen (HBeAg)-negative patients with either TAF or TDF. Study 110 randomized and treated 873 HBeAg-positive patients with either TAF or TDF. Both studies met their primary endpoint of noninferiority to TDF based on the percentage of patients with chronic hepatitis B with plasma HBV DNA levels less than 29 IU/mL at 48 weeks of therapy. In an integrated analysis of both studies, TAF-treated patients showed improvements in certain bone and renal laboratory parameters compared with TDF-treated patients. TAF-treated patients also had numerically higher rates of normalization of blood serum alanine aminotransferase levels (83% versus 75% [Study 108] and 72% versus 67% [Study 110]). Both analogues were generally well tolerated with a 1% adverse event discontinuation rate. The most common adverse events reported were abdominal pain, back pain, cough, fatigue, headache, and nausea occurring in similar rates in both treatment groups.

Sources: Gilead, Vemlidy prescribing information, Food and Drug Administration