Pharmaceutical Approval Update

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Arakoda (tafenoquine) tablets

**Manufacturer:** 60 Degrees Pharmaceuticals (60P), Washington, D.C.

**Date of Approval:** August 9, 2018

**Indication:** Arakoda is indicated for the prophylaxis of malaria in patients aged 18 years and older.

**Drug Class:** An oral antimalarial

**Uniqueness of Drug:** Tafenoquine is the first new drug for preventing malaria to be approved by the FDA in more than 18 years. This agent was originally discovered by scientists at the Walter Reed Army Institute of Research. This approval was based on a concerted effort by the U.S. Army and 60P, involving more than 21 clinical trials with more than 3,100 trial subjects.

**Contraindications:** Tafenoquine is contraindicated in patients with G6PD deficiency or unknown G6PD status; in breastfeeding by a lactating woman when the infant is found to be G6PD-deficient or if the G6PD status is not known; in patients with a history of psychotic disorders or current psychotic symptoms; and in patients with a known hypersensitivity to tafenoquine, other 8-aminoquinolines, or any component of tafenoquine.

**Warnings and Precautions:**

**Hemolytic anemia.** G6PD testing must be performed before prescribing tafenoquine due to the risk of hemolytic anemia. Because of the limitations with G6PD tests, physicians need to be aware of the residual risk of hemolysis; adequate medical support and follow-up to manage hemolysis should be available. Patients should be monitored for signs or symptoms of hemolysis. The drug should be discontinued if hemolysis occurs.

**G6PD deficiency in pregnancy or lactation.** Tafenoquine may cause fetal harm if administered to a pregnant woman with a G6PD-deficient fetus. Tafenoquine is not recommended for use during pregnancy. A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to tafenoquine through breast milk. An infant’s G6PD status should be checked prior to breastfeeding.

**Methemoglobinemia.** Asymptomatic elevations in blood methemoglobin have been observed in clinical trials. Initiate appropriate therapy if signs or symptoms of methemoglobinemia occur. Patients with NADH-dependent methemoglobin reductase deficiency should be carefully monitored.

**Psychiatric effects.** Serious psychiatric adverse reactions have been observed in patients with a history of psychosis or schizophrenia, at doses different from the approved dose. If psychotic symptoms such as hallucinations, delusions, or grossly disorganized thinking or behavior occur, discontinuation of tafenoquine should be considered. Patients should be evaluated by a mental health professional as soon as possible.

Subjects with a history of psychiatric disorders were excluded from three of five clinical trials when tafenoquine was compared to mefloquine.

**Hypersensitivity reactions.** Serious hypersensitivity reactions, including angioedema and urticaria, have been observed during clinical trials of tafenoquine. If a hypersensitivity reaction occurs, appropriate therapy should be instituted.

**Delayed adverse reactions including the prior noted reactions.** Due to the long half-life of tafenoquine (approximately 17 days), there may be a delay in the onset and/or duration of psychiatric effects, hemolytic anemia, methemoglobinemia, and/or hypersensitivity reactions.

**Drug interactions.** Tafenoquine should not be used concomitantly with drugs that are substrates of organic cation transporter-2 (OCT2) or multidrug and toxin extrusion (MATE) transporters.

**Use in special populations.** The use of tafenoquine in breastfeeding women during treatment and for three months after the last dose is not recommended in a G6PD-deficient infant or in an infant with an unknown G6PD status.

The pharmacokinetics of tafenoquine have not been studied in individuals with renal or hepatic dysfunction.

**Dosing and Administration:** Tafenoquine should be administered with food. A loading regimen of 200 mg (2 x 100-mg tablets) should be given on each of the three days before travel into a malarious region. The maintenance regimen of 200 mg once weekly (starting seven days after the last loading regimen dose) should be given while in the malarious region. The terminal prophylaxis regimen of 200 mg one time, given seven days after the last maintenance dose, should be given in the week following exit from the malarious region.

**Commentary:** The efficacy of tafenoquine was demonstrated in three double-blind, randomized, controlled studies. In Trial 1, in an area of holoendemic P. falciparum malaria in Kenya, 123 subjects were randomized to different regimens of tafenoquine after taking a three-day presumptive course of halofantrine to eliminate any existing parasitemia. After 15 weeks, 75% were parasitemia-free compared to 8% of placebo-treated patients. Protective efficacy was conferred on 73% of the studied individuals. Trial 2 included 187 semi-immune residents of a malarious region in Ghana. After treating existing parasitemia with doxycycline/primaquine/quinine, the subjects were randomized into prophylactic groups including tafenoquine and placebo. After 12 weeks, 73% were parasitemia-free compared to 6% of placebo-treated patients. Protective efficacy was conferred on 71% of the studied individuals. Trial 3 compared tafenoquine with mefloquine for the prophylaxis of both P. falciparum and P. vivax malaria in healthy, non-immune soldiers deployed to East Timor (now Timor-Leste). Within 26 weeks, no one had developed malaria, providing supportive evidence of efficacy. The most common adverse reactions in clinical trials (incidence ≥1%) were: abnormal dreams, anxiety, back pain, depression, diarrhea, dizziness, head-

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Ache, increased alanine aminotransferase (ALT), insomnia, motion sickness, nausea, and vomiting.

**Source:** 60 Degrees Pharmaceuticals, Arakoda prescribing information.

**Annovera (segesterone acetate and ethinyl estradiol vaginal system)**

**Manufacturer:** The Population Council Inc., New York, NY

**Date of Approval:** August 10, 2018

**Indication:** Annovera is indicated for females of reproductive potential to prevent pregnancy. This agent has not been adequately evaluated in females with a body mass index of > 29 kg/m².

**Drug Class:** A progestin/estrogen-combination hormonal contraceptive

**Uniqueness of Drug:** Having access to a variety of contraceptive options allows women to choose the method that best suits them. In low-resource settings, women encounter unique obstacles to getting effective contraception. Public-sector programs, the main source of contraception in most developing countries, typically offer limited options with limited supplies. Health-care providers are not always available or trained in providing counseling and/or services for women’s reproductive health needs. For these reasons, women are at risk for unintended pregnancy, unsafe abortion, and other health risks associated with childbirth and pregnancy. The segesterone acetate and ethinyl estradiol vaginal system (Annovera) is the first in a new class of contraceptives. The soft, reusable, flexible 2.25 inches-in-diameter silicone ring can be inserted and removed by a woman herself. It is left in place for 21 days then removed for 7 days and is indicated to prevent pregnancy for up to one year. It does not require refrigeration, making it vital for low-resource setting use and distribution.

**Contraindications:** Annovera is contraindicated in patients with a high risk of arterial or venous thrombotic diseases; current or a history of breast cancer or other estrogen- or progestin-sensitive cancer(s); liver tumors, acute hepatitis, or severe (decompensated) cirrhosis; undiagnosed abnormal uterine bleeding; hypersensitivity to any of Annovera’s components; and/or use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

**Warnings and Precautions:**

**Boxed warning:** Cigarette smoking and serious cardiovascular events. Cigarette smoking increases the risk of serious cardiovascular events from using combination hormonal contraceptive (CHC) products. This risk increases with age, particularly in women aged 35 years and over, and also with the number of cigarettes smoked. For this reason, CHCs should not be used by women who smoke and are over 35 years old.

**Thrombotic disorders and other vascular problems.** Annovera should be stopped if a thrombotic or thromboembolic event occurs. It should be stopped at least four weeks before and through two weeks following major surgery. Annovera should be started no sooner than four weeks after delivery, in woman who are not breastfeeding. The cardiovascular risk factors for women, especially those over 35 years old, should be considered before initiating Annovera.

**Liver disease.** If jaundice develops, Annovera should be discontinued.

**Risk of liver enzyme elevations with concomitant hepatitis C treatment.** Annovera should be stopped prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir. Once this regimen has been completed, Annovera can be restarted after two weeks.

**Hypertension.** Annovera should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. If women with well-controlled hypertension use Annovera, their blood pressure should be closely monitored. Annovera should be stopped if the blood pressure rises significantly.

**Carbohydrate and lipid metabolic effects.** In prediabetic and diabetic women using Annovera, their blood glucose should be closely monitored. Alternative contraceptive methods should be considered in women with uncontrolled dyslipidemias.

**Headache.** Patients should be evaluated for significant changes in headaches. Annovera should be discontinued if indicated.

**Bleeding irregularities and amenorrhea.** Annovera may cause irregular bleeding or amenorrhea. If irregular bleeding or amenorrhea continues, the patient should be evaluated for other causes.

**Use in special populations.** Annovera should be discontinued if pregnancy occurs. Lactation is not recommended for nursing mothers on Annovera as it can decrease milk production.

**Drug interactions.** Drugs or herbal products that induce certain enzymes, including CYP3A4, may increase breakthrough bleeding and/or decrease the effectiveness of Annovera. Patients should be counseled to use a backup or alternative contraceptive method when taking concomitant enzyme inducers.

**Availability, Dosage, and Administration:** Annovera is a silicone elastomer vaginal system containing 105 mg of segesterone acetate and 17.4 mg of ethinyl estradiol. It releases on average 0.15 mg/day of segesterone acetate and 0.013 mg/day of ethinyl estradiol. One Annovera is inserted into the vagina by following the directions in the patient’s instructions for use. The vaginal system must remain in place continuously for three weeks (21 days) followed by a one-week (seven-day) vaginal system-free interval. One vaginal system provides contraception for thirteen 28-day cycles (one year).

**Commentary:** FDA approval of Annovera was based in part on data from 17 clinical trials, including two pivotal phase 3 safety and efficacy trials. The phase 3 program enrolled women (N = 2,308) across 27 United States study sites, and in Australia, Europe, and Latin America. Women were aged between 18 and 40 years. They were instructed to use the Annovera system over 13 menstrual cycles, or one full year. Based on pooled data from the two trials, 2,111 females ≤ 35 years of age completed 17,427 evaluable 28-day cycles (cycles in which no back-up contraception was used). The pooled pregnancy rate was 2.98. The study results showed that Annovera was 97.3% effective in preventing pregnancy when used as directed. Return to fertility was assessed in 290 of the subjects, who either desired pregnancy or switched to a nonhormonal method after the trials, and all 290 subjects reported a return to fertility during the six-month follow-up period (defined as a return of menses or pregnancy). The most common adverse reactions (> 5%)
in clinical trials were lower/upper abdominal pain, breast tenderness/pain/discomfort, diarrhea, dysmenorrhea, genital pruritus, headache/migraine, mycotic infection/candidiasis, nausea/vomiting, urinary tract infection, vaginal discharge, and vulvovaginal bleeding irregularities, including metrorrhagia.


**Oxervate (cenegermin-bkbj) ophthalmic solution 0.002%**

**Manufacturer:** Dompé Farmaceutici S.p.A., L’Aquila, Italy  
**Date of Approval:** August 22, 2018  
**Indication:** Cenegermin-bkbj is indicated for the treatment of neurotrophic keratitis.  
**Drug Class:** A nerve-growth factor  
**Uniqueness of Drug:** Neurotrophic keratitis is a degenerative disease that leads to a loss of corneal sensation, which impairs corneal health. This loss causes progressive corneal damage to the top layer, including corneal thinning, ulceration, and perforation in severe cases. It is estimated that the prevalence of neurotrophic keratitis occurs in fewer than five in 10,000 individuals. Cenegermin is the first drug to be approved to treat neurotrophic keratitis. Previously, patients with this disease often had to utilize surgical interventions, which were usually only palliative.

**Contraindications:** None  
**Warnings and Precautions:**  
Patients should remove contact lenses prior to administering cenegermin. Patients should wait 15 minutes after instilling cenegermin drops before reinserting contact lenses.  
**Availability and Dosage:** Cenegermin ophthalmic solution is available as 0.002% (20 mcg/mL) in a multidose vial. The drug should be administered as one drop in the affected eye(s), six times daily at two-hour intervals, for eight weeks.

**Handling and Storage:** The weekly carton should be removed from the insulated container. It should be stored for up to 14 days in a refrigerator (no later than five hours from when it is received from the pharmacist). If treatment is started immediately after receiving the weekly carton, wait until the first vial is thawed (which may take up to 30 minutes when kept at room temperature up to 77°F [25°C]), since it is stored in the freezer in the pharmacy. The vial should not be shaken. Once opened, the vial can be kept in the original weekly carton in the refrigerator between 36°F and 46°F (2°C to 8°C) for up to 12 hours or at room temperature up to 77°F (25°C), in which case it must be used within 12 hours. After 12 hours at room temperature, patients should discard the vial with any unused amount. Follow the provided instructions for use to administer the drug and answer any further questions.

**Commentary:** The safety and efficacy of cenegermin were studied in patients (N = 151) with neurotrophic keratitis in two eight-week, randomized, controlled, multicenter double-blind studies. Patients were randomized into different groups (cenegermin 10 mcg/mL or vehicle). All eye drops in both studies were given six times daily in the affected eye(s) for eight weeks. In the first study, only patients with the disease in one eye were enrolled, while in the second study, patients with the disease in both eyes were treated in both eyes. The mean patient age was 61–65 years old (range, 18–95 years old). Sixty-one percent of patients were female. Complete corneal healing in eight weeks was demonstrated in 70% of cenegermin-treated patients compared to 28% of vehicle-treated (placebo) patients. The most common adverse reactions (incidence > 5%) in clinical trials were ocular hyperemia, ocular pain, eye inflammation, and increased lacrimation. Cenegermin was granted a Priority Review designation and an Orphan Drug designation.