Twirla®
(levonorgestrel and ethinyl estradiol)
transdermal system
120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol

A contraceptive patch purposefully designed for her

Introducing Twirla®, the first and only combined hormonal once-weekly birth control patch delivering a low dose of estrogen.[1-5]

INDICATION AND USAGE

TWIRLA is indicated as a method of contraception for use in women of reproductive potential with a BMI <30 kg/m^2 for whom a combined hormonal contraceptive is appropriate.

Limitations of Use:

Consider the reduced effectiveness of TWIRLA in women with a BMI ≥25 to <30 kg/m^2 before prescribing TWIRLA. TWIRLA is contraindicated in women with a BMI ≥30 kg/m^2.

IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI ≥30 kg/m^2

Cigarette Smoking and Serious Cardiovascular Events

Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including TWIRLA, are contraindicated in women who are over 35 years of age and smoke.

Contraindicated in Women with a BMI ≥30 kg/m^2

TWIRLA is contraindicated in women with a BMI ≥30 kg/m^2. Compared to women with a lower BMI, women with a BMI ≥30 kg/m^2 had reduced effectiveness and may have a higher risk for venous thromboembolic events (VTEs).

CONTRAINDICATIONS

TWIRLA is contraindicated and should not be used in women with a high risk of arterial or venous thrombotic disease, including women with a BMI ≥30 kg/m^2; headaches with focal neurological symptoms, migraine with aura, women over 35 years of age with any migraine headache; liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis, or liver disease; undiagnosed abnormal uterine bleeding; pregnancy; current or history of breast cancer or other estrogen- or progestin-sensitive cancer; hypersensitivity to any components of TWIRLA; and use of hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir with or without dasabuvir.

WARNINGS AND PRECAUTIONS

- **Thromboembolic Disorders and Other Vascular Conditions –** Women are at increased risk for a VTE when using TWIRLA.
  - Stop TWIRLA if an arterial or VTE occurs.
  - Stop TWIRLA if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
  - Discontinue TWIRLA during prolonged immobilization and, if feasible, stop TWIRLA at least 4 weeks before and through 2 weeks after major surgery.
  - Start TWIRLA no earlier than 4 weeks after delivery in women who are not breast-feeding.
  - Before starting TWIRLA, evaluate any past medical history or family history of thromboembolism or thromboembolic disorders and consider whether history suggests inherited or acquired hypercoagulopathy.

  Arterial Events – CHCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke, particularly among older women (>35 years of age), smokers, and women with hypertension, dyslipidemia, diabetes, or obesity.
- **Liver Disease –** Discontinue TWIRLA if jaundice develops.
- **Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment –** Discontinue TWIRLA prior to starting therapy with the hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. TWIRLA can be restarted approximately 2 weeks following completion of treatment with that combination drug regimen.
- **Hypertension –** Monitor blood pressure at routine visits and stop TWIRLA if blood pressure rises significantly. An increase in blood pressure has been reported in women using CHCs, and this increase is more likely in older women with extended duration of use.
- **Gallbladder Disease –** Studies suggest CHCs increase the risk of developing gallbladder disease and may also worsen existing gallbladder disease.
- **Adverse Carbohydrate and Lipid Metabolic Effects –**
  - TWIRLA may decrease glucose tolerance. Carefully monitor prediabetic and diabetic women who are using TWIRLA.
  - Consider alternative contraception for women with uncontrolled dyslipidemia. TWIRLA may cause adverse lipid changes. Women with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using TWIRLA, which may increase the risk of pancreatitis.
- **Headache –** If a woman using TWIRLA develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue TWIRLA as indicated. Consider discontinuation of TWIRLA if there is any increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event).
- **Bleeding Irregularities and Amenorrhea –** Women using TWIRLA may experience unscheduled bleeding, especially during the first 3 months of use, or experience absence of scheduled bleeding. If bleeding persists or occurs after previously regular cycles on TWIRLA, or if scheduled bleeding does not occur, evaluate for causes such as pregnancy or, in the case of unscheduled bleeding, malignancy.
- **Other Warnings and Precautions –** Other warnings and precautions include depression, cervical cancer, increased serum concentrations of binding globulins, hereditary angioedema, and chloasma.

ADVERSE REACTIONS

The following serious adverse reactions occurred in <1% of women who received TWIRLA: cholelithiasis, cholecystitis, major depression, suicidal ideation, appendicitis, ectopic pregnancy, pneumonia, and gastroenteritis. A total of 4 VTEs in TWIRLA-treated patients were identified in the phase 3 clinical trial. The most common adverse reactions (≥2%) in clinical trials for TWIRLA are application site disorders, nausea, headache, dysmenorrhea, and increased weight.

Patients should be counseled that TWIRLA does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of TWIRLA or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with TWIRLA.

This is not a comprehensive list of safety information related to TWIRLA.

Please see full Prescribing Information, including BOXED WARNING.

To report **SUSPECTED ADVERSE REACTIONS**, call 1-855-389-4752 or report via the FDA MedWatch Program at www.fda.gov/medwatch or 1-800-FDA-1088.

References: 1. Nelson AL, Kaunitz AM, Kroll R, et al. Efficacy, safety, and tolerability of a levonorgestrel/ethinyl estradiol transdermal delivery system: phase 3 clinical trial results. *Contraception*. 2021;103(3):137-143. **2.** Twirla [prescribing information]. Princeton, NJ: Agile Therapeutics, Inc.; 2020. **3.** Xulane [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals; 2020. **4.** Zafemy [prescribing information]. Bridgewater, NJ: Amneal Pharmaceuticals LLC; 2021. **5.** Centers for Disease Control and Prevention. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Morb Mortal Wkly Rep.* 2016;65(3):1-103.

Agile® THERAPEUTICS

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