RXADVANCE
2 Park Central Drive
Southborough, MA 01772

NEW DRUG APPROVAL

Brand Name	TWIRLA®
Generic Name	levonorgestrel and ethinyl estradiol
Drug Manufacturer	Agile Therapeutics, Inc

New Drug Approval

TWIRLA® indicated as a method of contraception for use in women of reproductive potential with a BMI < 30 kg/m2 for whom a combined hormonal contraceptive is appropriate.

FDA Approval date: Feb 14, 2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Contraception is the act of preventing pregnancy. Methods include medications, procedures, devices, and behaviors.

In 2015–2017, 64.9% of the 72.2 million women aged 15–49 in the United States were currently using contraception. The most common contraceptive methods currently used were female sterilization (18.6%), oral contraceptive pill (12.6%), long-acting reversible contraceptives (LARCs) (10.3%), and male condom (8.7%).

Current contraceptive use increased with age, from 37.2% among women aged 15–19 to 73.7% among women aged 40–49.

The percentage of non-Hispanic white women currently using contraception (67.0%) was higher compared with non-Hispanic black women (59.9%), but not different from the percentage for Hispanic women (64.0%).

Use of LARCs was higher among women aged 20–29 (13.1%) compared with women aged 15–19 (8.2%) and 40–49 (6.7%); use was also higher among women aged 30–39 (11.7%) compared with those aged 40–49.

Efficacy

Efficacy of TWIRLA® was evaluated in one open label, single arm, multicenter trial in the United States

(NCT # NCT02158572) of one-year duration that enrolled 2,031 women, ranging in age between 18 and 60 years, who were healthy and sexually active with regular menstrual cycles.

For the primary efficacy analysis, 1,736 women between the ages 18 and 35 years completed 15,165 evaluable 28-day cycles with TWIRLA®, where no back-up contraception was used, and sexual intercourse occurred.

The racial/ethnic distribution for the primary analysis was White (67%), Black/African American (24%), Asian

(4%), American Indian/Alaskan Native (0.5%), Native Hawaiian/Pacific Islander (0.5%), Other/Multiple races

(5%); 19% of the study population were Hispanic. The mean age was 26 years.

The mean BMI in the primary efficacy analysis group was 28.3 kg/m2, and 35.3% of subjects had a BMI ≥ 30

kg/m2. The primary efficacy endpoint was the Pearl Index (PI) defined as the pregnancy rate per 100 woman-years of use.

The overall PI for the primary analysis population (TWIRLA®-treated patients) was 5.8 (95% CI 4.5, 7.2). There were clear differences in efficacy by BMI category:

NEW DRUG APPROVAL

TWIRLA® has demonstrated reduced efficacy in women with a BMI > 25 and < 30 kg/m2.

BMI	Pearl Index (95% CI)
< 25 kg/m2	3.5 (1.8 – 5.2)
≥ 25 and < 30 kg/m2	5.7 (3.0 – 8.4)
≥ 30 kg/m2	8.6 (5.8 – 11.5)

Safety

ADVERSE EVENTS

The most common adverse reactions (≥ 2%) in clinical trials for TWIRLA® are application site disorders, nausea, headache, dysmenorrhea, and increased weight.

WARNINGS & PRECAUTIONS

- Vascular Risks: Stop TWIRLA® if a thromboembolic event occurs. Stop TWIRLA® at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. Consider cardiovascular risk factors before initiating in all women, particularly those over 35 years.
- Liver Disease: Discontinue TWIRLA® if jaundice occurs.
- Risk of Liver Enzyme Elevations with Concomitant Hepatitis C
- Hypertension: If used in women with well-controlled hypertension, monitor blood pressure and stop use if blood pressure rises significantly.
- Gallbladder Disease: May cause or worsen gallbladder disease.
- Adverse Carbohydrate and Lipid Metabolic Effect: Monitor glucose in prediabetic and diabetic women using TWIRLA®. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia.
- Headache: Evaluate significant change in headaches and discontinue TWIRLA® if indicated.
- Uterine Bleeding: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist.
- Retinal vein thrombosis has been reported, discontinue use if unexplained partial or complete loss of vision, diplopia, proptosis, papilledema, or retinal vascular lesions develop.
- Hypertriglyceridemia, current or family history; increased risk of pancreatitis.
- Binding globulins, including thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin, serum concentrations may be increased; replacement thyroid hormone or cortisol therapy may need to be increased.
- Headache or migraine that is recurrent, persistent, or severe; exacerbation or new onset; discontinue and evaluate cause

CONTRAINDICATIONS

- High risk of arterial or venous thromboembolism diseases.
- Breast cancer or other estrogen- or progestin-sensitive cancer
- Contraindicated in Women with a BMI ≥ 30 kg/m2
- Liver tumors, acute viral hepatitis or decompensated cirrhosis
- Undiagnosed abnormal uterine bleeding
- Pregnancy
- Hypersensitivity reactions to components of TWIRLA®
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir

NEW DRUG APPROVAL

Clinical Pharmacology

MECHANISMS OF ACTION

Combination hormonal contraceptives lower the risk of becoming pregnant primarily by suppressing ovulation.

Dose & Administration

ADULTS

TWIRLA®(R), Should be given to women who has BMI less than 30 kg/m(2)

- Apply 1 patch transdermally and wear for 7 consecutive days; reapply each week (on Patch Change Day) for 3 consecutive weeks; do not wear a patch during week 4 (menstruation; patch-free week); repeat a new 28-day (4-week) cycle on the day after week 4 ends.
- **No current use of hormonal contraception:** Apply first patch during the first 24 hours of menstruation; nonhormonal backup required for the first 7 days of that cycle only.
- **Switching from combination oral contraception**: Finish current pill cycle and apply first patch on the day the next pill cycle would normally start, ensure pregnancy has not occurred prior to starting the patch. If patch is applied more than 7 days after taking the last active pill, nonhormonal backup contraception should be used during the first 7 days of patch use.
- **Switching from transdermal system or vaginal ring:** Finish patch or vaginal ring cycle and apply first TWIRLA®(R) patch on the day the next cycle would normally start, ensure pregnancy has not occurred prior to starting TWIRLA®(R). If patch is applied more than 7 days after removal of the patch or ring, nonhormonal backup contraception should be used during the first 7 days of TWIRLA®(R) patch use.
- **Switching from injection, intrauterine system, implant, or progestin-only pill**: Apply first patch on the day the next injection would start, the day of intrauterine system or implant removal, or on the day the next progestin-only pill cycle would start.

May initiate within the first 5 days of a first trimester abortion or miscarriage without additional backup contraception. Use nonhormonal contraception and follow instructions for initiation if after 5 days; do not initiate earlier than 4 weeks after second trimester abortion or miscarriage, or childbirth in women who elect not to breastfeed

PEDIATRICS

Safety and effectiveness of TWIRLA® as a method of contraception have been established in females of reproductive potential with a BMI < 30 kg/m2. Efficacy is expected to be the same in postmenarcheal females regardless of age. TWIRLA® is not indicated in females before menarche.

GERIATRICS

TWIRLA® has not been studied in postmenopausal women and is not indicated in this population.

RENAL IMPAIRMENT

There are no dosage adjustments provided (has not been studied). Use with caution and monitor blood pressure closely.

HEPATIC IMPAIRMENT

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of TWIRLA®. Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal and CHC causation has been excluded.

NEW DRUG APPROVAL

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Transdermal patch: 120 mcg/day levonorgestrel (LNG) and 30 mcg/day ethinyl estradiol (EE)