Twirla® (levonorgestrel/ethinyl estradiol) – New drug approval

- On February 14, 2020, Agile Therapeutics' announced the FDA approval of Twirla (levonorgestrel/ethinyl estradiol), as a method of contraception for use in women of reproductive potential with a body mass index (BMI) < 30 kg/m^2 for whom a combined hormonal contraceptive is appropriate.

    — Twirla's reduced effectiveness in women with a BMI ≥ 25 to < 30 kg/m^2 should be considered before prescribing Twirla.

- The efficacy of Twirla was established in one open label, single arm study 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 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 was 5.8 (95% CI 4.5, 7.2). There were clear differences in efficacy by BMI category as shown in the table below.

BMI	Number of evaluable cycles	PI (95% CI)
< 25 kg/m^2	6,007	3.5 (1.8, 5.2)
≥ 25 and < 30 kg/m^2	3,881	5.7 (3.0, 8.4)
≥ 30 kg/m^2	5,264	8.6 (5.8, 11.5)

- Twirla carries boxed warnings for cigarette smoking and serious cardiovascular events and contraindicated in women with a BMI ≥ 30 kg/m^2.

- Twirla is also contraindicated in patients with:

    — High risk of arterial or venous thromboembolism diseases
    — Breast cancer or other estrogen- or progestin-sensitive cancer
    — 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.

- Additional warnings and precautions for Twirla include thromboembolic disorders and other vascular conditions; liver disease; risk of liver enzyme elevations with concomitant hepatitis C treatment; hypertension; age-related considerations; gallbladder disease; adverse carbohydrate and lipid metabolic effects; headache; bleeding irregularities and amenorrhea; depression; cervical cancer; effect on binding globulins; hereditary angioedema; and chloasma.

- The most common adverse reactions (≥ 2%) with Twirla use were application site disorders, nausea, headache, dysmenorrhea, and increased weight.

- The Twirla transdermal system (TDS) is used in a 28-day (four-week) cycle. A new TDS is applied and worn for seven days for three consecutive weeks (weeks 1, 2, and 3). No TDS is worn during week 4 (the TDS-free week), when withdrawal bleeding is expected.

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    - — On the day after week 4 ends, a new 28-day cycle is started by applying a new TDS. Under no circumstances should there be more than a 7-day TDS-free interval between dosing cycles.
    - — Twirla should be applied to one of the following sites: abdomen, buttock or upper torso (excluding breasts).

- Agile Therapeutics plans to launch Twirla in the fourth quarter of 2020. Twirla will be available as a 120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol TDS.