

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204017Orig1s000

Trade Name: Twirla transdermal system.

Generic or Proper Name: Twlevonorgestrel and ethinyl estradiol

Sponsor: Agile Therapeutics, Inc.

Approval Date: February 14, 2020

Indication: For use by females of reproductive potential to prevent pregnancy.

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APPROVAL LETTER



NDA 204017

NDA APPROVAL

Agile Therapeutics, Inc.
Attention: Robert Conway
Senior Vice President
101 Poor Farm Road, 3rd Floor
Princeton, NJ 08540

Dear Mr. Conway:

Please refer to your New Drug Application (NDA) dated April 12, 2012, received April 13, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Twirla (levonorgestrel and ethinyl estradiol) transdermal system.

We acknowledge receipt of your amendment dated May 16, 2019, which constituted a complete response to our December 21, 2017, action letter.

We acknowledge receipt of your major amendment dated November 12, 2019, which extended the goal date by three months.

This new drug application provides for the use of Twirla (levonorgestrel and ethinyl estradiol) transdermal system for use by females of reproductive potential to prevent pregnancy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your January 17, 2020, submission containing final printed carton and container labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of fatal and non-fatal venous thromboembolism (VTE) and arterial thromboembolism.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

- 3785-1: A controlled, non-interventional, prospective, observational cohort study comparing the risks for fatal and non-fatal venous thromboembolism (VTE) and arterial thromboembolism (ATE) in new users of Twirla to new users of oral combined hormonal contraceptives (CHCs) (primary comparator) and new users of Xulane (secondary comparator) in U.S. women of reproductive age using CHCs primarily for contraceptive reasons. The study should be designed to detect a 1.5 to 2-fold increased risk for VTE in new users of Twirla and adequately measure and control for possible confounders, especially age, BMI, and smoking status, among others.

The timetable you submitted on February 6, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2020
Final Protocol Submission:	11/2021
Interim Safety Analysis Report:	11/2026
Study Completion:	11/2031
Final Report Submission:	11/2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit clinical protocol(s) to your IND 057731 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:
Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3785-2: A clinical study in a minimum of 25 women to accurately assess the residual drug content and strength of Twirla. This study will evaluate Twirla worn by study subjects and analyze the ethinyl estradiol (EE) and levonorgestrel (LNG) content after prescribed wear and monitor adhesion over the entire wear period.

The timetable you submitted on February 6, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2020

Final Protocol Submission: 09/2020

Study/Trial Completion: 06/2021

Final Report Submission: 09/2021

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

*Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*⁴

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶ For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.⁷

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Include a section in your quarterly safety reports on transdermal system (TDS) related events. This section should capture the number of TDS replacements provided through your replacement program and the reason for the replacement (if provided by the patient).

This separate section should also include all TDS-related adverse events reported including TDS irritation, adhesion failure and any allergic reactions.

Submit this section as part of your quarterly safety reports for a period of at least 3 years following launch of TWIRLA in the US.

If you have any questions, please contact Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

Sincerely,

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

⁴ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁷ <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert
 - Instructions for Use
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AUDREY L GASSMAN
02/14/2020 04:36:13 PM