

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

213950Orig1s000

Generic or Proper Name: Norelgestromin and Ethinyl Estradiol
Transdermal System, 150/35 mcg per day

Sponsor: Amneal Pharmaceuticals LLC.

Approval Date: March 1, 2021

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213950Orig1s000

CONTENTS

Reviews / Information Included in this ANDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
Bioequivalence Review(s)	X
Chemistry Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

APPROVAL LETTER



ANDA 213950

ANDA APPROVAL

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 18, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day.¹

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

This corrected letter is being issued to correct minor editorial issues. This letter is identical to the February 25, 2021 approval letter except for the minor editorial revisions. This letter supersedes our previous February 25, 2021 approval letter. The date for approval letter remains unchanged.

Reference is also made to the complete response letter issued by this office on August 14, 2020, and to any amendments thereafter.

Reference is also made to FDA's (CGT) Designation – Grant letter dated December 16, 2019.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**. We have determined your Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day, to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Ortho Evra Transdermal System, of Janssen Pharmaceuticals, Inc. (Janssen).

We note that Amneal Pharmaceuticals LLC (Amneal) was granted a CGT designation for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day. Amneal is the “first approved applicant” for such competitive generic therapy, as defined in section 505(j)(5)(B)(v)(III) of the FD&C Act. Therefore, with this approval, Amneal is eligible for 180 days of CGT exclusivity for Norelgestromin and Ethinyl Estradiol

Transdermal System, 150/35 mcg per day, under section 505(j)(5)(B)(v) of the FD&C Act. This exclusivity will begin to run from the date of the first commercial marketing of the CGT (including the commercial marketing of the listed drug) by Amneal, as specified in section 505(j)(5)(B)(v) of the FD&C Act. Furthermore, in accordance with section 505(j)(5)(B)(v)(I) of the FD&C Act, this 180-day CGT exclusivity will not block approval of other applications until Amneal has commenced commercial marketing. Please submit a correspondence to this ANDA informing the Agency of the date you begin commercial marketing. Please also submit notice of first commercial marketing via e-mail to the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov. This e-mail should be sent the same day you commence commercial marketing. Reference is also made to the Special Forfeiture Rule for Competitive Generic Therapy in section 505(j)(5)(D)(iv) of the FD&C Act. Please be aware that, pursuant to this forfeiture rule, you will forfeit your eligibility for the 180-day CGT exclusivity period for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day, if you fail to market this CGT within 75 days after the date on which the approval of this application is made effective.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts; therefore, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. 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 package insert (PI), Medication Guide, and patient PI (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

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 (available at: <https://www.fda.gov/media/128163/download>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-form-fda-2253-and-request-advisory-comment-submissions>.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions² with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of

misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <https://www.fda.gov/media/71211/download>. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug’s labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled “Changes to an Approved NDA or ANDA” at <https://www.fda.gov/media/71846/download>.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

¹ We note that the reference listed drug (RLD) upon which you have based this ANDA, Janssen’s Ortho Evra Transdermal System, is no longer being marketed in the United States and is currently listed in the discontinued section of FDA’s *Approved Drug Products With Therapeutic Equivalence Evaluations* (the “Orange Book”). The Agency has determined that Janssen’s Ortho Evra Transdermal System, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in the *Federal Register* (80 FR 58489; September 29, 2015). This determination allows the Agency to approve ANDAs for the discontinued drug product.

² Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Catherine
Poole

Digitally signed by Catherine Poole

Date: 3/01/2021 07:46:03AM

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**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

213950Orig1s000

OTHER ACTION LETTERS



ANDA 213950

COMPLETE RESPONSE

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 18, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

BIOEQUIVALENCE

After reviewing your submitted justifications in the amendment dated June 12, 2020, we still have concerns on the significant lower concentration of ethinyl estradiol (EE) in your test product at 168 hours compared to Xulane® in your pivotal fasting BE study (No. ESTN/2018/1607). We acknowledge that based on the inclusion of data from 72 subjects in the pharmacokinetic and statistical analyses, the mean concentration for the test product (i.e., 29.5 pg/ml) at 168 hours is within the C_{ss} target range of 25-75 pg/ml of EE for optimum efficacy identified by the innovator of the reference listed drug, Ortho Evra®[1]. However, the data show that the EE concentrations for 38.9% (28 subjects) of the total subjects at 168 hours were lower than 25 pg/ml for the test product, compared to 16.7% (12 subjects) of the total subjects for the reference product. This difference in EE concentration between the test and reference products may lead to subjects experiencing sub-therapeutic EE levels. The agency requests that you provide an explanation along with supportive information for why the difference in EE concentrations is not expected to have an impact on the safety or efficacy of the drug product.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

DRUG SUBSTANCE, DRUG PRODUCT, PROCESS, BIOPHARMACEUTICS, FACILITY INSPECTION, CLINICAL BIOEQUIVALENCE, LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure that your ANDA addresses all listed patents and exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR AMENDMENT**, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

**RESUBMISSION
MINOR
COMPLETE RESPONSE AMENDMENT
BIOEQUIVALENCE**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Uzoma Nnebe, Regulatory Project Manager, Division of Project Management, at (240) 402 - 5828.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Mandy
Kwong

Digitally signed by Mandy Kwong

Date: 8/14/2020 04:35:43PM

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

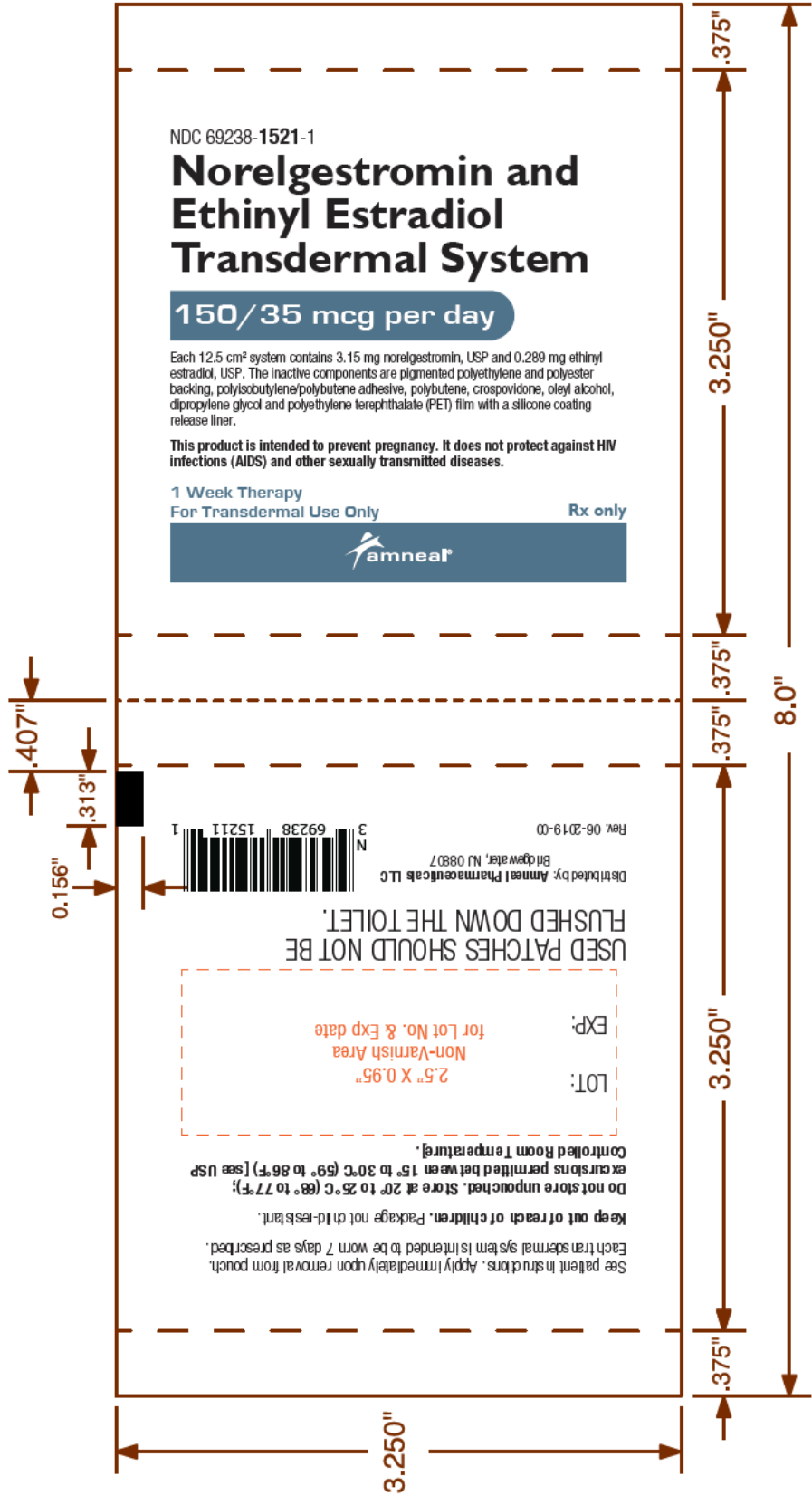
LABELING

Ethinyl Estradiol
150/35 mcg per day 150/35
Norelgestromin and Ethinyl Estradiol
50/35 mcg per day 150/35 mcg per day
Norelgestromin and Ethinyl Estradiol
per day 150/35 mcg per day 150/35
Norelgestromin and Ethinyl Estradiol
50/35 mcg per day 150/35 mcg per day
Norelgestromin and Ethinyl Estradiol

Label Size: 12.5 cm²

PROOF 1: 03.12.19

PMS 161- label brown



NDC 69238-1521-1

Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

Each 12.5 cm² system contains 3.15 mg norelgestromin, USP and 0.289 mg ethinyl estradiol, USP. The inactive components are pigmented polyethylene and polyester backing, polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol, dipropylene glycol and polyethylene terephthalate (PET) film with a silicone coating release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

1 Week Therapy For Transdermal Use Only Rx only



Rev. 06-2019-00
 Distributed by: Amneal Pharmaceuticals LLC
 Bridgewater, NJ 08807

USED PATCHES SHOULD NOT BE FLUSHED DOWN THE TOILET.

LOT: 2.5" X 0.95"
 Non-Varnish Area
 for Lot No. & Exp date
 EXP:

Controlled Room Temperature].
 Do not store unpouched. Store at 20° to 25° C (68° to 77°F); excursions permitted between 15° to 30° C (59° to 86°F) [see USP

Keep out of reach of children. Package not child-resistant.
 See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Size: 3.25" x 3.25"

PROOF 1: 06.13.19



(b) (4)

(b) (4)

0126275A

(b) (4)

Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Package not child-resistant. Keep out of reach of children.

Do not store unpouched. Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Note your Patch Change Day here

- Sunday
- Monday
- Tuesday
- Wednesday
- Thursday
- Friday
- Saturday

Place RX Label Here

Distributed by: Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 06-2019-00



Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

3 Transdermal Systems

NDC 69238-1521-3

Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

NDC 69238-1521-3

Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

Each 12.5 cm² system contains 3.15 mg norelgestromin, USP and 0.289 mg ethinyl estradiol, USP. The inactive components are pigmented polyethylene and polyester backing, polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol, dipropylene glycol and polyethylene terephthalate (PET) film with a silicone coating release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

For Transdermal Use Only
Contents: 3 Transdermal Systems

Rx only



Norelgestromin and Ethinyl Estradiol Transdermal System

150/35 mcg per day

3 Transdermal Systems

3.45" X 0.75"
Non-Varnish Area
for Lot No. & Exp date



1 2 3 Order refill Week off

Place these stickers on your **calendar**.

Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your **pouches**.

First Patch Second Patch Third Patch Order refill

amneal Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807
Rev. 06-2019-00

FPO Barcode Area

Label Size 3.25" x 3.25"

PROOF 1: 06.14.19



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL SYSTEM.

NORELGESTROMIN AND ETHINYL ESTRADIOL transdermal system

Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI $\geq$ 30 kg/m²

See full prescribing information for complete boxed warning.

- Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women over 35 years old who smoke. Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (4, 5.1)
- Norelgestromin and ethinyl estradiol transdermal system is contraindicated for use in women with a BMI $\geq$ 30 kg/m². Women with a BMI $\geq$ 30 kg/m² who use norelgestromin and ethinyl estradiol transdermal system may have a higher risk of venous thromboembolic events compared with women with a lower BMI. (4, 5.1, 8.8)

-----RECENT MAJOR CHANGES-----

Boxed Warning	4/2020
Indications and Usage (1)	4/2020
Contraindications (4)	4/2020
Warnings and Precautions (5.1)	4/2020
Warnings and Precautions (5.2)	4/2020

-----INDICATIONS AND USAGE-----

Norelgestromin and ethinyl estradiol transdermal system is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women with a BMI < 30 kg/m² for whom a combined hormonal contraceptive is appropriate. (1)

Limitations of Use: Norelgestromin and ethinyl estradiol transdermal system may be less effective in preventing pregnancy in women at or above 198 lbs (90 kg). (1, 4, 14)

-----DOSAGE AND ADMINISTRATION-----

- Norelgestromin and ethinyl estradiol transdermal system uses a 28-day (four-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for three weeks (21 total days). Week Four is patch-free. (2.1, 2.3)
- Apply each new patch on the same day of the week. Wear only one patch at a time. (2.1)
- Do not cut or alter the patch in any way. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Transdermal system: 150 mcg/day norelgestromin, USP and 35 mcg/day ethinyl estradiol, USP. (3)

-----CONTRAINDICATIONS-----

- At high risk of arterial or venous thromboembolic events (4)
- BMI $\geq$ 30 kg/m² (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

-----WARNINGS AND PRECAUTIONS-----

- Vascular risks: Stop norelgestromin and ethinyl estradiol if a thrombotic event occurs. Stop 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. (5.1)
- Liver disease: Discontinue norelgestromin and ethinyl estradiol if jaundice occurs. (5.3)
- High blood pressure: Do not prescribe norelgestromin and ethinyl estradiol for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking norelgestromin and ethinyl estradiol. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- Headache: Evaluate significant change in headaches and discontinue norelgestromin and ethinyl estradiol if indicated. (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.9)

-----ADVERSE REACTIONS-----

The most frequent adverse reactions reported during clinical trials ($\geq$ 5%) were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of CHCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with CHCs. (7.1)

-----USE IN SPECIFIC POPULATIONS-----

- Nursing mothers: Not recommended; can decrease milk production. (8.3)

**See 17 for PATIENT COUNSELING INFORMATION
and FDA-approved patient labeling.**

Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: CIGARETTE SMOKING AND SERIOUS
CARDIOVASCULAR EVENTS and
CONTRAINDICATED IN WOMEN WITH A BMI $\geq$ 30
kg/m²

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 How to Use Norelgestromin and Ethinyl Estradiol Transdermal System
- 2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System
- 2.3 How to Apply Norelgestromin and Ethinyl Estradiol Transdermal System

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Thromboembolic Disorders and Other Vascular Conditions
- 5.2 Ethinyl Estradiol Exposure
- 5.3 Liver Disease
- 5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment
- 5.5 High Blood Pressure
- 5.6 Gallbladder Disease
- 5.7 Carbohydrate and Lipid Metabolic Effects
- 5.8 Headache
- 5.9 Bleeding Irregularities
- 5.10 Hormonal Contraceptive Use Before or During Early Pregnancy
- 5.11 Depression
- 5.12 Carcinoma of Breasts and Cervix
- 5.13 Effect on Binding Globulins
- 5.14 Monitoring
- 5.15 Hereditary Angioedema
- 5.16 Chloasma

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on Combined Hormonal Contraceptives
- 7.2 Effects of Combined Hormonal Contraceptives on Other Drugs
- 7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation
- 7.4 Interference with Laboratory Tests

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment
- 8.8 BMI and Weight Considerations

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

- 16.1 How Supplied
- 16.2 Special Precautions for Storage and Disposal

17 PATIENT COUNSELING INFORMATION

- 17.1 General

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI ≥ 30 kg/m²

- **Cigarette Smoking and Serious Cardiovascular Events**

Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive 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 norelgestromin and ethinyl estradiol transdermal system, are contraindicated in women who are over 35 years of age and smoke [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

- **Contraindicated in Women with a BMI ≥ 30 kg/m²**

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with a BMI ≥ 30 kg/m². The risk of VTE may be greater with norelgestromin and ethinyl estradiol transdermal system in women with a BMI > 30 kg/m² compared to women with a lower BMI [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

Norelgestromin and ethinyl estradiol transdermal system is indicated for the prevention of pregnancy in women with a body mass index (BMI) < 30 kg/m² for whom a combined hormonal contraceptive is appropriate.

Limitations of Use:

Norelgestromin and ethinyl estradiol transdermal system may be less effective in preventing pregnancy in women who weigh 198 lbs (90 kg) or more. Norelgestromin and ethinyl estradiol transdermal system is contraindicated for use in women with BMI ≥ 30 kg/m² [see *Contraindications (4)*, *Warnings and Precautions (5.1)* and *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, norelgestromin and ethinyl estradiol transdermal system must be used exactly as directed.

Complete instructions to facilitate patient counseling on proper system usage may be found in the FDA-Approved Patient Labeling.

2.1 How to Use Norelgestromin and Ethinyl Estradiol Transdermal System

The norelgestromin and ethinyl estradiol transdermal system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free. Withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the “Patch Change Day.” For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

Do not cut, damage or alter the norelgestromin and ethinyl estradiol transdermal patch in any way. If the norelgestromin and ethinyl estradiol transdermal patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week Four ends, a new four-week cycle is started by applying a new patch. Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.

2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System

There are multiple options for starting the norelgestromin and ethinyl estradiol transdermal system, and the woman should choose the option that is most appropriate (see Table 1):

Table 1: Instructions for Administration

Starting norelgestromin and ethinyl estradiol transdermal system in women with no current use of hormonal contraception	
The woman has two options for starting the patch and she should choose the option that is right for her:	
First Day Start	
- The woman should apply her first patch during the first 24 hours of her menstrual period. If a patch is applied after the first 24 hours of menstruation, non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) is needed for the first 7 days of the first cycle only. - The woman should apply a new patch each week for three weeks (21 total days). Every new patch should be applied on the same day of the week. This day is known as the “Patch Change Day.” For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. - No patch is worn during Week Four (the “Patch-Free Week”). Withdrawal bleeding is expected during this time. - On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.	
Sunday Start	
- The woman should apply her first patch on the first Sunday after her menstrual period begins. - With this option, a non-hormonal backup method of birth control, such as a condom and spermicide or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. - If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.	
Switching from another contraceptive method	
Oral combination hormonal contraception (oral CHC)	- If the woman is switching from the pill to norelgestromin and ethinyl estradiol transdermal system, she should complete her current pill cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally start her next pill - If she does not get her period within a week after taking the last active pill, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. - If the patch is applied more than a week after taking the last active pill, she should use a non-hormonal back-up contraception (such as

	condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.
Transdermal system	• If the woman is switching from another contraceptive transdermal system to norelgestromin and ethinyl estradiol transdermal system, she should complete the current transdermal system cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next transdermal system cycle would normally start. • If she does not get her period within a week after removing the last transdermal system, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. If norelgestromin and ethinyl estradiol transdermal system is applied more than a week after removal of the last patch, non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Vaginal ring	• If the woman is switching from the vaginal ring to norelgestromin and ethinyl estradiol transdermal system, she should complete her current vaginal ring cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally insert her next vaginal ring. • If she does not get her period within a week after removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. • If the patch is applied more than a week after removal of the last vaginal ring, she should use a non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.
Injection	• If the woman is switching from an injection contraceptive to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next injection would normally occur.
Intrauterine system (IUS)	• If the woman is switching from an intrauterine system to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of IUS removal. If the IUS is not removed on the first day of the menstrual cycle, non-hormonal backup contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Implant	• If the woman is switching from an implant to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of implant removal.
Progestin-only pill	• If the woman is switching from a progestin-only pill to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next progestin-only pill cycle would normally start.

Use after Childbirth

Start contraceptive therapy with norelgestromin and ethinyl estradiol transdermal system in women who elect not to breastfeed no sooner than 4 weeks after childbirth due to increased risk of thromboembolism. If a woman begins using norelgestromin and ethinyl estradiol transdermal system postpartum, and has not yet had a period, consider the possibility of ovulation and conception occurring prior to use of norelgestromin and ethinyl estradiol transdermal system, and instruct her to use an additional method of contraception, such as a condom and spermicide or diaphragm and spermicide, for the first seven days [see *Warnings and Precautions (5.1)* and *Pregnancy (8.1)*].

Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs in the first trimester, norelgestromin and ethinyl estradiol transdermal system may be started immediately. An additional method of contraception is not needed if norelgestromin and ethinyl estradiol transdermal system is started immediately. If use of norelgestromin and ethinyl estradiol transdermal system is not started within 5 days following a first trimester abortion, the woman should follow the instructions for a woman starting norelgestromin and ethinyl estradiol transdermal system for the first time. In the meantime she should be advised to use a non-hormonal contraceptive method. Ovulation may occur within 10 days of an abortion or miscarriage.

Start norelgestromin and ethinyl estradiol transdermal system no earlier than 4 weeks after a second trimester abortion or miscarriage, due to the increased risk of thromboembolic disease [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

2.3 How to Apply Norelgestromin and Ethinyl Estradiol Transdermal System

CHOOSING A PLACE ON THE BODY TO PUT THE PATCH



- The patch may be placed on the upper outer arm, abdomen, buttock or back in a place where it won't be rubbed by tight clothing. For example, it should not be placed under the waistband of clothing.
- The patch should not be placed on the breasts, on cut or irritated skin, or on the same location as the previous patch.

Before applying the patch:

- The woman should make sure the skin is clean and dry.
- She should not use lotions, creams, oils, powders, or make-up at the patch site. It may cause the patch to fail to stick properly or to become loose.

HOW TO APPLY THE PATCH

	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.

- The woman should check her patch every day to make sure all edges are sticking correctly.

WHEN TO CHANGE THE NORELGESTROMIN AND ETHINYL ESTRADIOL TRANSDERMAL PATCH

- The patch works for seven days (one week). The woman should apply a new patch on the same day each week (her Patch Change Day) for 3 weeks in a row. She must make sure she has removed her old patch prior to applying the new patch.
- During Week 4, she **DOES NOT** wear a patch. She must make sure she removes her old patch. (Her period should begin during this week.)
- Following Week 4, she repeats the cycle of three weekly applications followed by a patch-free week.

WHAT IF THE PATCH BECOMES LOOSE OR FALLS OFF?

The patch must stick securely to the skin to work properly. If the norelgestromin and ethinyl estradiol transdermal patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs. The woman should not try to reapply a patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it.

If a patch edge lifts up:

- The woman should press down firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. She should run her fingers over the entire surface area to smooth out any “wrinkles” around the edges of the patch.
- If her patch does not stick completely, she should remove it and apply a replacement patch.
- She should not tape or wrap the patch to her skin or reapply a patch that is partially adhered to clothing.

If the patch has been off or partially off:

- **For less than 1 Day**, she should try to reapply it. If the patch does not adhere completely, she should apply a new patch immediately. (No backup contraception is needed and her Patch Change Day will stay the same).
- **For more than 1 Day or if she is not sure for how long**, she may not be protected from pregnancy. To reduce this risk, she should apply a new patch and start a new 4-week cycle. She will now have a new Patch Change Day and **MUST USE NON-HORMONAL BACKUP CONTRACEPTION** (such as a condom and spermicide or diaphragm and spermicide) for the first week of her new cycle.

IF THE WOMAN FORGETS TO CHANGE HER PATCH

- **at the start of any patch cycle (Week One/Day 1): SHE MAY NOT BE PROTECTED FROM PREGNANCY.** She should apply the first patch of her new cycle as soon as she remembers. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception, such as a condom and spermicide or diaphragm and spermicide, for the first week of the new cycle.
- **in the middle of the patch cycle (Week Two/Day 8 or Week Three/Day 15),**
 - for **one or two days** (up to 48 hours), she should apply a new patch immediately. The next patch should be applied on the usual “Patch Change Day.” No back-up contraception is needed.
 - for more than two days (48 hours or more), **SHE MAY NOT BE PROTECTED FROM PREGNANCY.** She should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new “Patch Change Day” and a new “Day 1.” The woman must use back-up contraception for one week.
- **at the end of the patch cycle (Week Four/Day 22),**
 - If the woman forgets to remove her patch, she should take it off as soon as she remembers. The next cycle should be started on the usual “Patch Change Day,” which is the day after Day 28. No back-up contraception is needed.

Under no circumstances should there be more than a seven-day patch-free interval between cycles. If there are more than seven patch-free days, **THE WOMAN MAY NOT BE PROTECTED FROM PREGNANCY** and back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for seven days. As with combined oral contraceptives, the risk of ovulation increases with each day beyond the recommended drug-free period. If she has had intercourse during such an extended patch-free interval, consider the possibility of pregnancy.

Change Day Adjustment

If the woman wishes to change her Patch Change Day, she should complete her current cycle, removing the third norelgestromin and ethinyl estradiol transdermal patch on the correct day. During the patch-free week, she may select an earlier Patch Day Change by applying a new norelgestromin and ethinyl estradiol transdermal patch on the desired day. In no case should there be more than 7 consecutive patch-free days.

Breakthrough Bleeding or Spotting

In the event of unscheduled or breakthrough bleeding or spotting (bleeding that occurs on the days that norelgestromin and ethinyl estradiol transdermal system is worn), treatment should be continued. If unscheduled bleeding persists longer than a few cycles, consider causes other than norelgestromin and ethinyl estradiol transdermal system.

If the woman does not have scheduled or withdrawal bleeding (bleeding that should occur during the patch-free week), she should resume treatment on the next scheduled Change Day. If norelgestromin and ethinyl estradiol transdermal system has been used correctly, the absence of withdrawal bleeding is not necessarily an indication of pregnancy. Nevertheless, consider the possibility of pregnancy, especially if absence of withdrawal bleeding occurs in 2 consecutive cycles. Discontinue norelgestromin and ethinyl estradiol transdermal system if pregnancy is confirmed.

In Case of Skin Irritation

If patch use results in uncomfortable irritation, the patch may be removed and a new patch may be applied to a different location until the next Change Day. Only one patch should be worn at a time.

Additional Instructions for Dosing

Unscheduled bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing hormonal contraceptives. In case of breakthrough bleeding, as in all cases of irregular bleeding from the vagina, consider nonfunctional causes. In case of undiagnosed persistent or recurrent abnormal bleeding from the vagina, take adequate diagnostic measures to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another method of contraception may solve the problem.

Use of Hormonal Contraceptives in the Event of a Missed Menstrual Period

1. If the woman has not adhered to the prescribed schedule, consider the possibility of pregnancy at the time of the first missed period. Discontinue use of norelgestromin and ethinyl estradiol transdermal system if pregnancy is confirmed.
2. If the woman has adhered to the prescribed regimen and misses one period, she should continue using her contraceptive patches. However, if she has adhered to the prescribed regimen, misses one period and has symptoms associated with pregnancy, rule out pregnancy. Discontinue norelgestromin and ethinyl estradiol transdermal system use if pregnancy is confirmed.
3. If the woman has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue norelgestromin and ethinyl estradiol transdermal system use if pregnancy is confirmed.

3 DOSAGE FORMS AND STRENGTHS

Transdermal system: 150 mcg/day norelgestromin, USP and 35 mcg/day ethinyl estradiol, USP.

4 CONTRAINDICATIONS

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with the following conditions:

- At high risk of arterial or venous thromboembolic events. Examples include women who:
 - Smoke, if over age 35 [see *Boxed Warning*, and *Warnings and Precautions (5.1)*]

- Have deep vein thrombosis or pulmonary embolism, now or in the past [*see Warnings and Precautions (5.1)*]
- Have inherited or acquired hypercoagulopathies [*see Warnings and Precautions (5.1)*]
- Have cerebrovascular disease [*see Warnings and Precautions (5.1)*]
- Have coronary artery disease [*see Warnings and Precautions (5.1)*]
- Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [*see Warnings and Precautions (5.1)*]
- Have uncontrolled hypertension [*see Warnings and Precautions (5.5)*]
- Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
- Have headaches with focal neurological symptoms or have migraine headaches with aura
 - Women over age 35 with any migraine headaches [*see Warnings and Precautions (5.8)*]
- Body Mass Index ≥ 30 kg/m² [*see Warnings and Precautions (5.1)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
- Pregnancy, because there is no reason to use hormonal contraceptives during pregnancy [*see Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.12)*]
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [*see Warnings and Precautions (5.4)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Conditions

- Stop norelgestromin and ethinyl estradiol transdermal system if an arterial or venous thromboembolic event (VTE) occurs.
- Stop norelgestromin and ethinyl estradiol transdermal system if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- If feasible, stop norelgestromin and ethinyl estradiol transdermal system at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Discontinue use of norelgestromin and ethinyl estradiol transdermal system during prolonged immobilization and resume treatment based on clinical judgment.
- Start norelgestromin and ethinyl estradiol transdermal system no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- Before starting norelgestromin and ethinyl estradiol transdermal system, evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy [*see Contraindications (4)*].

Arterial Events

The use of CHCs increases the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and women with

hypertension, dyslipidemia, diabetes, or obesity. Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women over 35 years of age who smoke [see *Contraindications (4)*]. Cigarette smoking increases the risk of serious cardiovascular events from CHC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

Venous Events

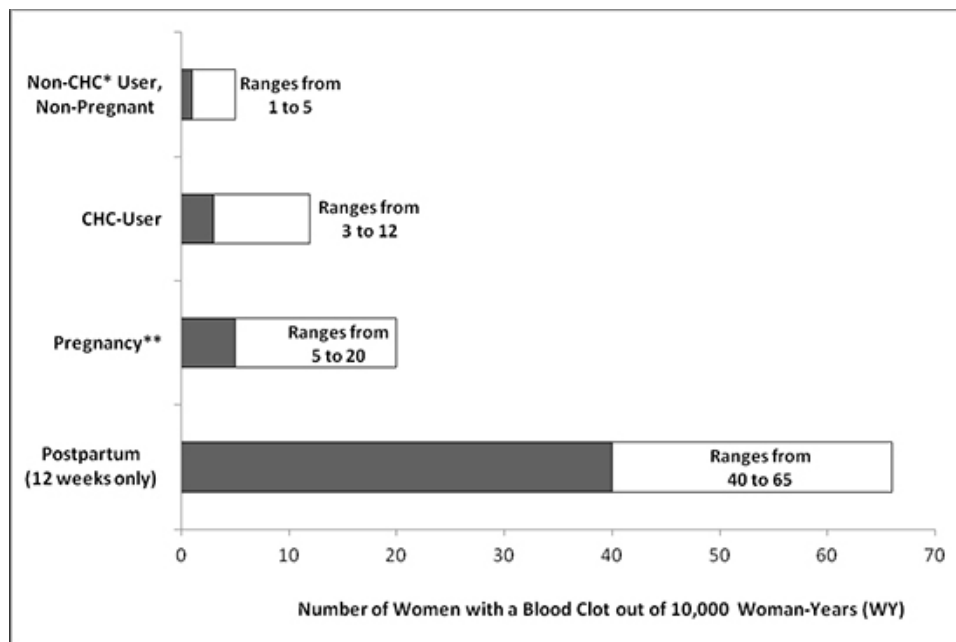
The use of CHCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs. The risk of VTE may be greater with norelgestromin and ethinyl estradiol transdermal system in women with a BMI ≥ 30 kg/m² compared to women with a lower BMI [see *Contraindications (4)*].

While the risk of VTE associated with the use of CHCs is well-established, the rates of VTE are even greater during pregnancy, and especially during the post-partum period (see Figure 1). The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. This initial higher risk declines during the first year, but users of CHCs remain at an increased risk of VTE compared to non-users of CHCs. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued.

Figure 1 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs with a range of doses and routes of administration, for pregnant women, and for women in the post-partum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 1: Likelihood of Developing a VTE Within One Year Among Pregnant and Non-Pregnant Women



*CHC = combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

5.2 Ethinyl Estradiol Exposure

Higher estrogen exposure may increase the risk of adverse reactions, including venous thromboembolism (VTE). The Area Under the Curve (AUC) for ethinyl estradiol (EE) is approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared to oral contraceptives containing EE 35 mcg. In contrast, the peak concentration (C_{max}) for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system [see *Clinical Pharmacology (12.3)*].

5.3 Liver Disease

Impaired Liver Function

Do not use norelgestromin and ethinyl estradiol in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver [see *Contraindications (4)*]. Discontinue norelgestromin and ethinyl estradiol if jaundice develops. 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.

Liver Tumors

Norelgestromin and ethinyl estradiol is contraindicated in women with benign and malignant liver tumors [see *Contraindications (4)*]. Hepatic adenomas are associated with CHC use. An estimate of the attributable risk is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) CHC users. However, the risk of liver cancers in CHC users is less than one case per million users.

5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as CHCs. Discontinue norelgestromin and ethinyl estradiol prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Norelgestromin and ethinyl estradiol can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.5 High Blood Pressure

Norelgestromin and ethinyl estradiol is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop norelgestromin and ethinyl estradiol if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking hormonal contraceptives, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease. A past history of CHC-related cholestasis predicts an

increased risk with subsequent CHC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take norelgestromin and ethinyl estradiol. CHCs may decrease glucose tolerance in a dose-related fashion. In a 6-cycle clinical trial with norelgestromin and ethinyl estradiol transdermal system there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on hormonal contraceptives.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraceptives.

5.8 Headache

If a woman taking norelgestromin and ethinyl estradiol develops new headaches that are recurrent, persistent or severe, evaluate the cause and discontinue norelgestromin and ethinyl estradiol if indicated.

Consider discontinuation of norelgestromin and ethinyl estradiol in the case of increased frequency or severity of migraine during hormonal contraceptive use (which may be prodromal of a cerebrovascular event).

5.9 Bleeding Irregularities

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough) bleeding and spotting sometimes occur in women using norelgestromin and ethinyl estradiol. Consider non-hormonal causes and take adequate diagnostic measures to rule out malignancy, other pathology, or pregnancy in the event of unscheduled bleeding, as in the case of any abnormal vaginal bleeding. If pathology and pregnancy have been excluded, time or a change to another contraceptive product may resolve the bleeding.

In the clinical trials, most women started their scheduled (withdrawal) bleeding on the fourth day of the drug-free interval, and the median duration of withdrawal bleeding was 5 to 6 days. On average, 26% of women per cycle had 7 or more total days of bleeding and/or spotting (this includes both scheduled and unscheduled bleeding and/or spotting). Three clinical studies of the efficacy of norelgestromin and ethinyl estradiol in preventing pregnancy assessed scheduled and unscheduled bleeding [see *Clinical Studies (14)*] in 3,330 women who completed 22,155 cycles of exposure. A total of 36 (1.1%) of the women discontinued norelgestromin and ethinyl estradiol at least in part, due to bleeding or spotting.

Table 2 summarizes the proportion of subjects who experienced unscheduled (breakthrough) bleeding/spotting by treatment cycle.

Table 2: Unscheduled (Breakthrough) Bleeding/Spotting (Subjects Evaluable for Efficacy)

Treatment Cycle	Pooled data from 3 studies N=3,319	
	n	% ^a
Cycle 1	2,994	18.2
Cycle 2	2,743	11.9
Cycle 3	2,699	11.6

Cycle 4	2,541	10.1
Cycle 5	2,532	9.2
Cycle 6	2,494	8.3
Cycle 7	698	8.3
Cycle 8	692	8.7
Cycle 9	654	8.6
Cycle 10	621	8.7
Cycle 11	631	8.9
Cycle 12	617	6.3
Cycle 13	611	8.0

^a Percentage of subjects with breakthrough bleeding/spotting events.

Amenorrhea and Oligomenorrhea

In the event of amenorrhea, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one patch or started the patch on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may encounter amenorrhea or oligomenorrhea after discontinuation of hormonal contraceptive use, especially when such a condition was pre-existent.

5.10 Hormonal Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue norelgestromin and ethinyl estradiol transdermal system use if pregnancy is confirmed.

Administration of CHCs should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.11 Depression

Carefully observe women with a history of depression and discontinue norelgestromin and ethinyl estradiol if depression recurs to a serious degree.

5.12 Carcinoma of Breasts and Cervix

Norelgestromin and ethinyl estradiol is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive [*see Contraindications (4)*].

There is substantial evidence that CHCs do not increase the incidence of breast cancer. Although some past studies have suggested that CHCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.13 Effect on Binding Globulins

The estrogen component of CHCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.14 Monitoring

A woman who is taking hormonal contraceptive should have routine visits with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.15 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.16 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while using norelgestromin and ethinyl estradiol.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of combination hormonal contraceptives, including norelgestromin and ethinyl estradiol, are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events, including venous and arterial thromboembolic events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.3)*]

Adverse reactions commonly reported by users of combination hormonal contraceptives are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to norelgestromin and ethinyl estradiol transdermal system in 3,330 sexually active women (3,322 of whom had safety data) who participated in three Phase 3 clinical trials designed to evaluate contraceptive efficacy and safety. These subjects received six or 13 cycles of contraception (norelgestromin and ethinyl estradiol transdermal system or an oral contraceptive comparator in 2 of the trials). The women ranged in age from 18 to 45 years and were predominantly white (91%).

The most common adverse reactions ($\geq 5\%$) reported during clinical trials were breast symptoms, nausea/vomiting, headache, application site disorder, abdominal pain, dysmenorrhea, vaginal bleeding and menstrual disorders, and mood, affect and anxiety disorders. The most common events leading to discontinuation were application site reaction, breast symptoms (including breast discomfort, engorgement and pain), nausea and/or vomiting, headache and emotional lability.

Adverse drug reactions reported by $\geq 2.5\%$ of norelgestromin and ethinyl estradiol-treated subjects in these trials are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by $\geq 2.5\%$ of Norelgestromin and Ethinyl Estradiol-treated Subjects in Three Phase 3 Clinical Trials

System/Organ Class* Adverse reaction	Norelgestromin and Ethinyl Estradiol (n=3,322)
Reproductive system and breast disorders	
Breast symptoms [†]	22.4%
Dysmenorrhea	7.8%
Vaginal bleeding and menstrual disorders [†]	6.4%
Gastrointestinal disorders	
Nausea	16.6%
Abdominal pain [†]	8.1%
Vomiting	5.1%
Diarrhea	4.2%
Nervous system disorders	
Headache	21.0%
Dizziness	3.3%
Migraine	2.7%
General disorders and administration site conditions	
Application site disorder [†]	17.1%
Fatigue	2.6%
Psychiatric disorders	
Mood, affect and anxiety disorders [†]	6.3%
Skin and subcutaneous tissue disorders	
Acne	2.9%
Pruritus	2.5%
Infections and infestations	
Vaginal yeast infection [†]	3.9%
Investigations	
Weight increased	2.7%

* MedDRA version 10.0

[†] Represents a bundle of similar terms

Additional adverse drug reactions that occurred in $< 2.5\%$ of norelgestromin and ethinyl estradiol transdermal system-treated subjects in the above clinical trials datasets are:

- **Gastrointestinal disorders:** Abdominal distension
- **General disorders and administration site conditions:** Fluid retention¹, malaise
- **Hepatobiliary disorders:** Cholecystitis
- **Investigations:** Blood pressure increased, lipid disorders¹
- **Musculoskeletal and connective tissue disorders:** Muscle spasms
- **Psychiatric disorders:** Insomnia, libido decreased, libido increased

- **Reproductive system and breast disorders:** Galactorrhea, genital discharge, premenstrual syndrome, uterine spasm, vaginal discharge, vulvovaginal dryness
- **Respiratory, thoracic and mediastinal disorders:** Pulmonary embolism
- **Skin and subcutaneous tissue disorders:** Chloasma, dermatitis contact, erythema, skin irritation

¹Represents a bundle of similar terms

6.2 Postmarketing Experience

The following adverse reactions (Table 4) have been identified during post-approval use of norelgestromin and ethinyl estradiol transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 4: Alphabetical List of Adverse Drug Reactions Identified During Postmarketing Experience with Norelgestromin and Ethinyl Estradiol by System Organ Class*

System Organ Class	Adverse Drug Reactions
Cardiac disorders	Myocardial infarction [†]
Endocrine disorders	Hyperglycemia, insulin resistance
Eye disorders	Contact lens intolerance or complication
Gastrointestinal disorders	Colitis
General disorders and administration site conditions	Application site reaction [†] , edema [†]
Hepatobiliary disorders	Blood cholesterol abnormal, cholelithiasis, cholestasis, hepatic lesion, jaundice cholestatic, low density lipoprotein increased
Immune system disorders	Allergic reaction [†] , urticaria
Investigations	Blood glucose abnormal, blood glucose decreased
Metabolism and nutrition disorders	Increased appetite
Neoplasms benign, malignant and unspecified (Incl. cysts and polyps)	Breast cancer [†] , cervix carcinoma, hepatic adenoma, hepatic neoplasm
Nervous system disorders	Dysgeusia, migraine with aura
Psychiatric disorders	Anger, emotional disorder, frustration, irritability
Reproductive system and breast disorders	Breast mass, cervical dysplasia, fibroadenoma of breast, menstrual disorder [†] , suppressed lactation, uterine leiomyoma
Skin and subcutaneous tissues disorders	Alopecia, eczema, erythema multiforme, erythema nodosum, photosensitivity reaction, pruritus generalized, rash [†] , seborrheic dermatitis, skin reaction
Vascular disorders	Arterial thrombosis [†] , cerebrovascular accident [†] , deep vein thrombosis [†] , hemorrhage intracranial [†] , hypertension, hypertensive crisis, pulmonary embolism [†] , thrombosis [†]

* MedDRA version 10.0

[†] Represents a bundle of similar terms

7 DRUG INTERACTIONS

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of CHCs and potentially diminish the effectiveness of CHCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with CHCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances Increasing the Plasma Concentrations of CHCs:

Co-administration of atorvastatin or rosuvastatin and certain CHCs containing EE increase AUC values for EE by approximately 20% to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

CHCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. CHCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, and temazepam. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of CHCs [see *Warnings and Precautions (5.13)*].

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer norelgestromin and ethinyl estradiol with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions (5.4)*].

7.4 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use hormonal contraceptives during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose hormonal contraceptives prior to conception or during early pregnancy.

The administration of hormonal contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Hormonal contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

The effects of norelgestromin and ethinyl estradiol in nursing mothers have not been evaluated and are unknown. When possible, advise the nursing mother to use other forms of contraception until she has completely weaned her child. Estrogen-containing CHCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of norelgestromin and ethinyl estradiol have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Norelgestromin and ethinyl estradiol has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

No studies with norelgestromin and ethinyl estradiol have been conducted in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of combined hormonal contraceptive use until markers of liver function return to normal and combined hormonal contraceptive causation has been excluded [*see Contraindications (4) and Warnings and Precautions (5.3)*].

8.7 Renal Impairment

No studies with norelgestromin and ethinyl estradiol have been conducted in women with renal impairment.

8.8 BMI and Weight Considerations

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with a BMI ≥ 30 kg/m² because of the potential increased risk of VTE [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

Norelgestromin and ethinyl estradiol may be less effective in preventing pregnancy in women who weigh 198 lbs or more [see *Clinical Studies (14)*].

10 OVERDOSAGE

Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in women. In case of suspected overdose, all norelgestromin and ethinyl estradiol transdermal patches should be removed and symptomatic treatment given.

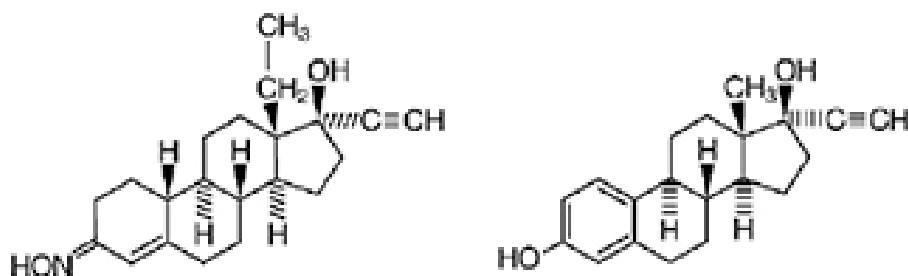
11 DESCRIPTION

Norelgestromin and ethinyl estradiol transdermal system has a contact surface area of 12.5 cm². It contains 3.15 mg norelgestromin, USP (NGMN) and 0.289 mg ethinyl estradiol, USP (EE), and its delivery rate is approximately 150 mcg of NGMN, USP and 35 mcg of EE, USP per day. Systemic exposures (as measured by area under the curve [AUC] and steady-state concentration [C_{ss}]) of NGMN, USP and EE, USP during use of norelgestromin and ethinyl estradiol transdermal system are higher and the C_{max} is lower than those produced by an oral contraceptive containing norgestimate, USP (NGM) 250 mcg / EE, USP 35 mcg [see *Boxed Warning* and *Clinical Pharmacology (12.3)*].

Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.

The outside of the backing layer is printed with “Norelgestromin and Ethinyl Estradiol 150/35 mcg per day” in brown ink.

The structural formulas of the components are:



Norelgestromin, USP

ethinyl estradiol, USP

Molecular weight, NGMN, USP: 327.47

Molecular weight, EE, USP: 296.41

Chemical name for NGMN, USP: 18, 19-Dinorepregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,3-oxime,(17 α)

Chemical name for EE, USP: 19-Norpregna-1,3,5(10)-trien-20-yne-3, 17-diol,(17 α)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

NGMN is the active progestin largely responsible for the progestational activity that occurs in women following application of norelgestromin and ethinyl estradiol transdermal system. NGMN is also the primary active metabolite produced following oral administration of NGM, the progestin component of some oral contraceptive products.

Combination hormonal contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

12.2 Pharmacodynamics

One clinical trial assessed the return of hypothalamic-pituitary-ovarian axis function post-therapy and found that follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol mean values, though suppressed during therapy, returned to near baseline values during the 6 weeks post therapy.

12.3 Pharmacokinetics

Absorption

The systemic delivery rate of NGMN and EE from norelgestromin and ethinyl estradiol transdermal system is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data. Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady-state is reached within 2 weeks of application. In one of the clinical studies, C_{ss} concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE.

Absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.

The mean (%CV) PK parameters C_{ss} and AUC_{0-168} for NGMN and EE following a single buttock application of norelgestromin and ethinyl estradiol transdermal system are summarized in Table 5.

In multiple dose studies, AUC₀₋₁₆₈ for NGMN and EE was found to increase over time (Table 5). In a three-cycle study, these PK parameters reached steady-state conditions during Cycle 3 (Figures 4 and 3). Upon removal of the patch, serum levels of EE and NGMN reach very low or non-measurable levels within 3 days.

Table 5: Mean (%CV*) PK Parameters of NGMN and EE Following 3 Consecutive Cycles of Norelgestromin and Ethinyl Estradiol Transdermal System Wear on the Buttock

Analyte	Parameter	Cycle 1 Week 1	Cycle 3 Week 1	Cycle 3 Week 2	Cycle 3 Week 3
NGMN	C _{ss} (ng/mL)	0.70 (39.4)	0.70 (41.8)	0.80 (28.7)	0.70 (45.3)
	AUC ₀₋₁₆₈ (ng·h/mL)	107 (44.2)	105 (43.2)	132 (43.4)	120 (43.9)
	t _{1/2} (h)	nc	nc	nc	32.1 (40.3)
EE	C _{ss} (pg/mL)	46.4 (38.5)	47.6 (36.4)	59.0 (42.5)	49.6 (54.4)
	AUC ₀₋₁₆₈ (pg·h/mL)	6,796 (39.3)	7,160 (40.4)	10,054 (41.8)	8,840 (58.6)
	t _{1/2} (h)	nc	nc	nc	21.0 (43.2)

nc = not calculated, *%CV is % of Coefficient of variation = 100 (standard deviation/mean)

Figure 2: Mean Serum NGMN Concentrations (ng/mL) in Healthy Female Volunteers Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal)

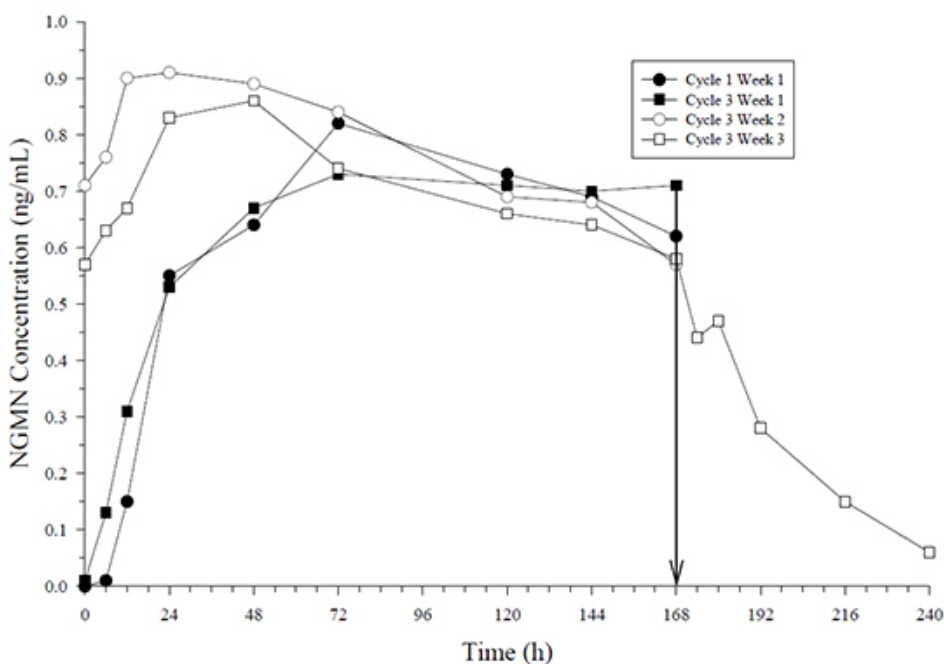
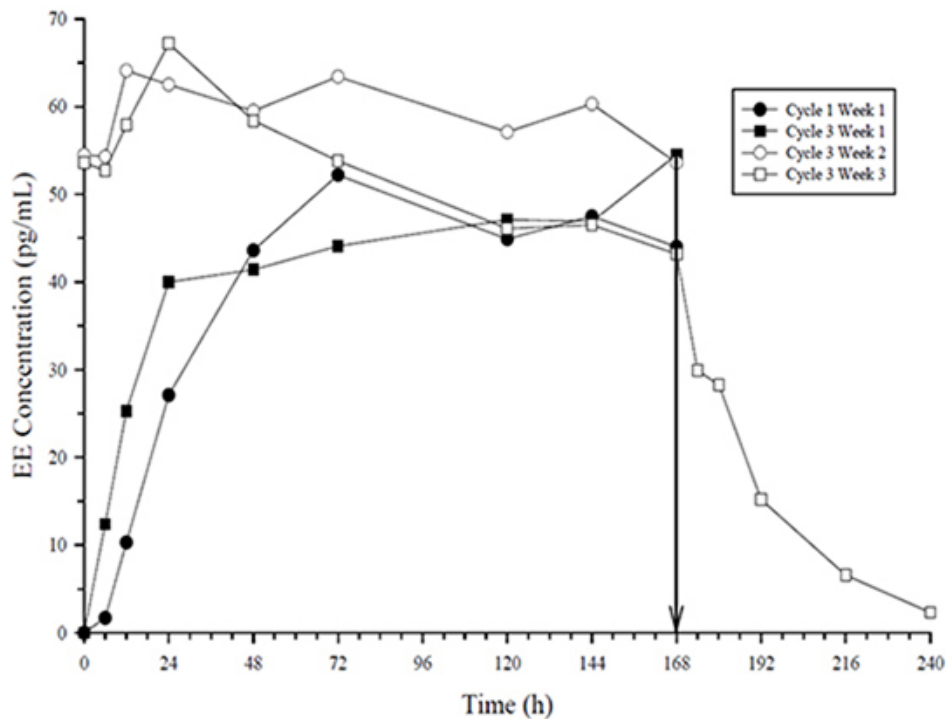


Figure 3: Mean Serum EE Concentrations (pg/mL) in Healthy Female Volunteers Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System on the Buttock for Three Consecutive Cycles (Vertical arrow indicates time of patch removal.)



The absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system was studied under conditions encountered in a health club (sauna, whirlpool and treadmill) and in a cold water bath.

The results indicated that for NGMN, there were no significant treatment effects on C_{ss} or AUC when compared to normal wear. For EE, increased exposures were observed due to sauna, whirlpool and treadmill. There was no significant effect of cold water on these parameters.

Results from a study of consecutive norelgestromin and ethinyl estradiol transdermal system wear for 7 days and 10 days indicated that serum concentrations of NGMN and EE dropped slightly during the first 6 hours after the patch replacement, and recovered within 12 hours. By Day 10 of patch administration, both NGMN and EE concentrations had decreased by approximately 25% when compared to Day 7 concentrations.

Metabolism

Since norelgestromin and ethinyl estradiol are delivered transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration does not occur. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Distribution

NGMN and norgestrel (a serum metabolite of NGMN) are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG, which limits its biological activity. EE is extensively bound to serum albumin and induces an increase in the serum concentrations of SHBG (see Table 5).

Elimination

Following removal of patches, the elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively. The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

Transdermal versus Oral Contraceptives

The norelgestromin and ethinyl estradiol transdermal patch delivers EE and NGMN over a seven-day period while oral contraceptives (containing NGM 250 mcg / EE 35 mcg) are administered on a daily basis. Figures 4 and 5 present mean PK profiles for EE and NGMN following administration of an oral contraceptive (containing NGM 250 mcg / EE 35 mcg) compared to the 7-day norelgestromin and ethinyl estradiol transdermal patch (containing NGMN 3.15 mg / EE 0.289 mg) during Cycle 2 in 32 healthy female volunteers.

Figure 4: Mean Serum Concentration-Time Profiles of NGMN Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of Norelgestromin and Ethinyl Estradiol Transdermal System for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Norelgestromin and Ethinyl Estradiol Transdermal System: Cycle 2, Week 3]

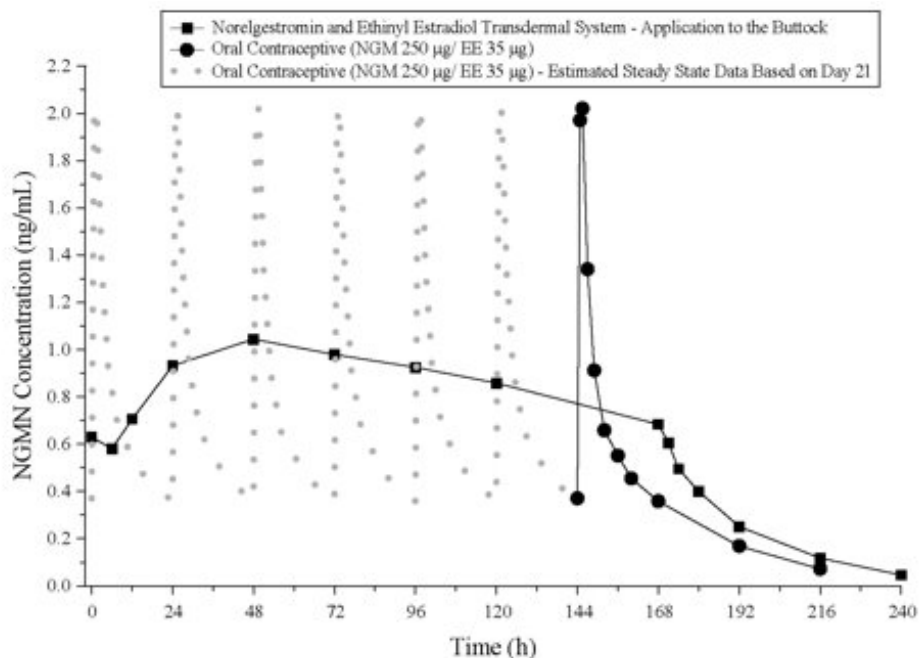


Figure 5: Mean Serum Concentration-Time Profiles of EE Following Once-Daily Administration of an Oral Contraceptive for 2 Cycles or Application of Norelgestromin and Ethinyl Estradiol Transdermal System for 2 Cycles to the Buttock in Healthy Female Volunteers. [Oral contraceptive: Cycle 2, Days 15 to 21, Norelgestromin and Ethinyl Estradiol Transdermal System: Cycle 2, Week 3]

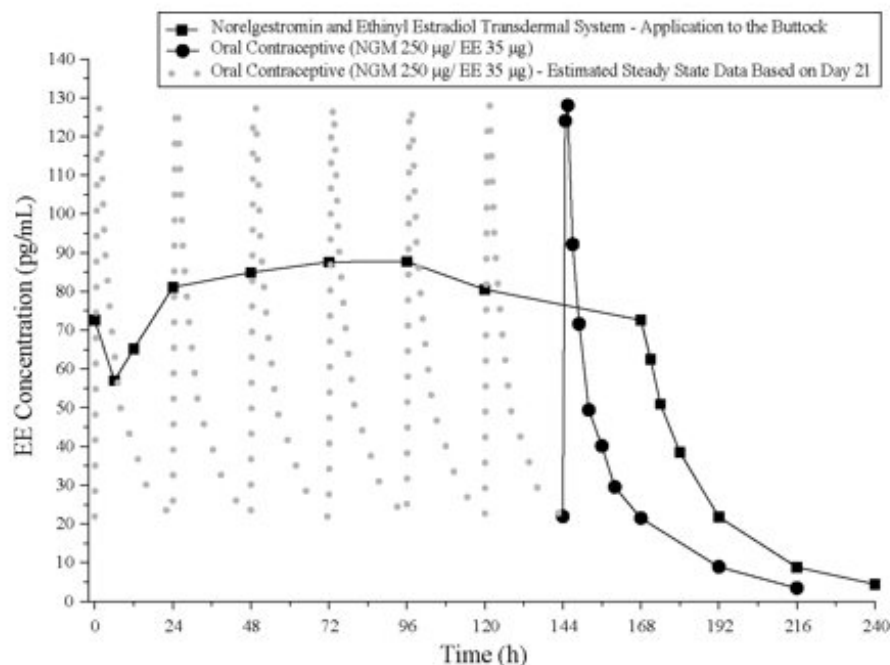


Table 6 provides the mean (%CV) for NGMN and EE pharmacokinetic (PK) parameters.

Table 6: Mean (%CV) NGMN and EE Steady-State Pharmacokinetic Parameters Following Application of Norelgestromin and Ethinyl Estradiol Transdermal System and Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) in Healthy Female Volunteers

Parameter	Norelgestromin and Ethinyl Estradiol Transdermal System*	ORAL CONTRACEPTIVE†
NGMN‡		
C_{max} (ng/mL)	1.12 (33.6)	2.16 (25.2)
AUC_{0-168} (ng·h/mL)	145 (36.8)	123 (30.2)§
C_{ss} (ng/mL)	0.888 (36.6)	0.732 (30.2)¶
EE		
C_{max} (pg/mL)	97.4 (31.6)	133 (27.7)
AUC_{0-168} (pg·h/mL)	12,971 (33.1)	8,281 (26.9)§
C_{ss} (pg/mL)	80.0 (33.5)	49.3 (26.9)¶

* Cycle 2, Week 3

† Cycle 2, Day 21

‡ NGM is rapidly metabolized to NGMN following oral administration

§ Average weekly exposure, calculated as $AUC_{24} \times 7$

¶ C_{avg}

In general, overall exposure for NGMN and EE (AUC and C_{ss}) was higher in subjects treated with norelgestromin and ethinyl estradiol transdermal system for both Cycle 1 and Cycle 2, compared to that for the oral contraceptive, while C_{max} values were higher in subjects administered the oral contraceptive. Under steady-state conditions, AUC_{0-168} and C_{ss} for EE were approximately 55% and 60% higher, respectively, for the

transdermal patch, and the C_{max} was about 35% higher for the oral contraceptive, respectively. Inter-subject variability (%CV) for the PK parameters following delivery from norelgestromin and ethinyl estradiol transdermal system was higher relative to the variability determined from the oral contraceptive. The mean PK profiles are different between the two products and caution should be exercised when making a direct comparison of these PK parameters.

In Table 7, percent change in concentrations (%CV) of markers of systemic estrogenic activity (Sex Hormone Binding Globulin [SHBG] and Corticosteroid Binding Globulin [CBG]) from Cycle 1 Day 1 to Cycle 1 Day 22 is presented. Percent change in SHBG concentrations was higher for norelgestromin and ethinyl estradiol transdermal system users compared to women taking the oral contraceptive; percent change in CBG concentrations was similar for norelgestromin and ethinyl estradiol transdermal system and oral contraceptive users. Within each group, the absolute values for SHBG were similar for Cycle 1, Day 22 and Cycle 2, Day 22.

Table 7: Mean Percent Change (%CV) in SHBG and CBG Concentrations Following Once-Daily Administration of an Oral Contraceptive (containing NGM 250 mcg / EE 35 mcg) for One Cycle and Application of Norelgestromin and Ethinyl Estradiol Transdermal System for One Cycle in Healthy Female Volunteers

Parameter	Norelgestromin and Ethinyl Estradiol Transdermal System (% change from Day 1 to Day 22)	ORAL CONTRACEPTIVE (% change from Day 1 to Day 22)
SHBG	334 (39.3)	200 (43.2)
CBG	153 (40.2)	157 (33.4)

Drug Interactions

In a PK drug interaction study, oral administration of tetracycline HCl, 500 mg four times daily for 3 days prior to and 7 days during wear of norelgestromin and ethinyl estradiol transdermal system did not significantly affect the PK of NGMN or EE.

Use in Specific Populations

Effects of Age, Body Weight, Body Surface Area and Race

The effects of age, body weight, body surface area and race on the PK of NGMN and EE were evaluated in 230 healthy women from nine pharmacokinetic studies of single 7-day applications of norelgestromin and ethinyl estradiol transdermal system. For both NGMN and EE, increasing age, body weight and body surface area each were associated with slight decreases in C_{ss} and AUC values. However, only a small fraction (10% to 25%) of the overall variability in the PK of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system may be associated with any or all of the above demographic parameters. There was no significant effect of race with respect to Caucasians, Hispanics and Blacks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

See *Warnings and Precautions* (5.3, 5.12) and *Use in Specific Populations* (8.1).

Norelgestromin was tested in *in vitro* mutagenicity assays (bacterial plate incorporation mutation assay, CHO/HGPRT mutation assay, chromosomal aberration assay using cultured human peripheral lymphocytes) and in one *in vivo* test (rat micronucleus assay) and found to have no genotoxic potential.

14 CLINICAL STUDIES

In 3 large clinical trials lasting 12 months, in North America, Europe and South Africa, 3,330 women (ages 18 to 45) completed 22,155 cycles of norelgestromin and ethinyl estradiol transdermal system use, the pregnancy rate in women aged 18 to 35 years was 1.07 (95% confidence interval 0.60, 1.76) per 100 woman-years of norelgestromin and ethinyl estradiol transdermal system use. The racial distribution was 91% Caucasian, 4.9% Black, 1.6% Asian, and 2.4% Other.

With respect to weight, 5 of the 15 pregnancies reported with norelgestromin and ethinyl estradiol transdermal system use were among women with a baseline body weight $\geq$ 198 lbs., which constituted < 3% of the study population. The greater proportion of pregnancies among women at or above 198 lbs. was statistically significant and suggests that norelgestromin and ethinyl estradiol transdermal system may be less effective in these women.

Patch Adhesion

In the clinical trials with norelgestromin and ethinyl estradiol transdermal system, approximately 2% of the cumulative number of patches completely detached and 3% partially detached. The proportion of subjects with at least 1 patch that completely detached ranged from 2% to 6%, with a reduction from Cycle 1 (6%) to Cycle 13 (2%). For instructions on how to manage detachment of patches, refer to *Dosage and Administration* (2).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP.

Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with “Norelgestromin and Ethinyl Estradiol 150/35 mcg per day” in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP.

Each transdermal system is packaged in a protective pouch.

Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems.

16.2 Special Precautions for Storage and Disposal

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Store patches in their protective pouches. Apply immediately upon removal from the protective pouch.

Do not store in the refrigerator or freezer.

Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

17.1 General

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from combined hormonal contraceptive use, and that women who are over 35 years old and smoke should not use combined hormonal contraceptives.
- The use of CHCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of CHCs. The risk of VTE in women using CHCs is 3 to 12 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to CHCs gradually disappears after use is discontinued.
- Norelgestromin and ethinyl estradiol does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- The Warnings and Precautions associated with combined hormonal contraceptives.
- Norelgestromin and ethinyl estradiol is not to be used during pregnancy; if pregnancy occurs during use of norelgestromin and ethinyl estradiol, instruct the patient to stop further use.
- Apply a single patch the same day every week (Weeks 1 through 3). Instruct patients what to do in the event a patch is missed. See “WHAT IF I FORGET TO CHANGE MY PATCH?” section in FDA-Approved Patient Labeling.
- Use a back-up or alternative method of contraception when enzyme inducers are used with norelgestromin and ethinyl estradiol.
- Combined hormonal contraceptives may reduce breast milk production; this is less likely to occur if breastfeeding is well established.
- Women who start combined hormonal contraceptives postpartum, and who have not yet had a period, should use an additional method of contraception until they have used a patch for 7 consecutive days.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles, amenorrhea in one cycle if the woman has not adhered to the dosing schedule, or if associated with symptoms of pregnancy, such as morning sickness or unusual breast tenderness.
- If the norelgestromin and ethinyl estradiol transdermal patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.
 - A patch should not be re-applied if it is no longer sticky, becomes stuck to itself or another surface, has other material stuck to it, or has become loose or fallen off before. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used.
 - A woman may not be protected from pregnancy if a patch is partially or completely detached for ≥ 24 hours (or if the woman is not sure how long the patch has been detached). She should start a new cycle immediately by applying a new patch. Back-up contraception, such as a condom and spermicide or diaphragm and spermicide, must be used for the first week of the new cycle.

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Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 02-2021-00

Patient Information

Norelgestromin (nor" el jes' troe min) and Ethinyl Estradiol (eth' i nil es" tra dye' ol) Transdermal System

What is the most important information I should know about norelgestromin and ethinyl estradiol transdermal system?

Do not use norelgestromin and ethinyl estradiol transdermal system if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control methods, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Do not use norelgestromin and ethinyl estradiol transdermal system if you have an increased risk for blood clots.

Do not use norelgestromin and ethinyl estradiol transdermal system if your Body Mass Index (BMI) is 30 kg/m² or more. Women with a BMI of 30 kg/m² or more who use norelgestromin and ethinyl estradiol transdermal system may be at a higher risk for developing blood clots compared to women with a BMI lower than 30 kg/m².

Hormonal birth control methods help to lower the chances of becoming pregnant. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

What is norelgestromin and ethinyl estradiol transdermal system?

Norelgestromin and ethinyl estradiol transdermal system is a birth control patch for women with a BMI less than 30 kg/m². It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norelgestromin.

Hormones from norelgestromin and ethinyl estradiol transdermal system get into the blood stream and are processed by the body differently than hormones from birth control pills. **You will be exposed to about 60% more estrogen if you use norelgestromin and ethinyl estradiol transdermal system than if you use a typical birth control pill containing 35 micrograms of estrogen.** In general, increased estrogen may increase the risk of side effects.

How well does norelgestromin and ethinyl estradiol transdermal system work?

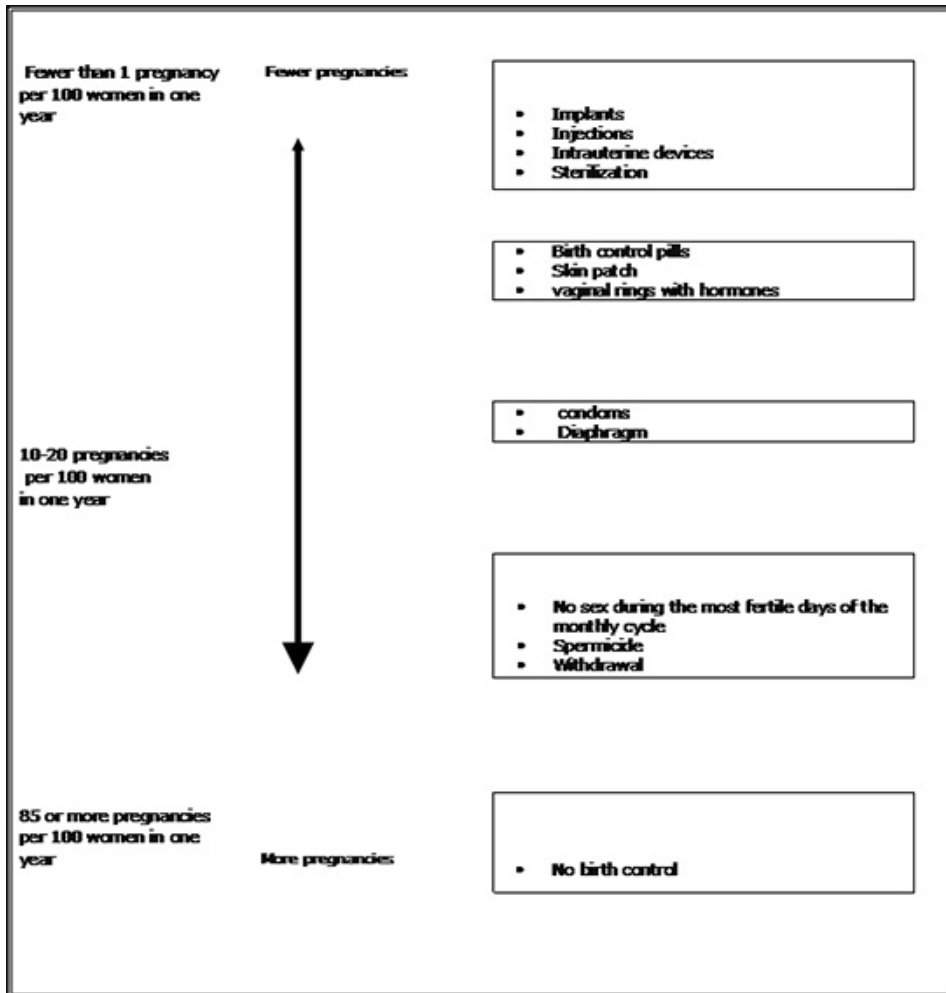
Your chance of getting pregnant depends on how well you follow the directions for using norelgestromin and ethinyl estradiol transdermal system. The better you follow the directions, the less chance you have of getting pregnant.

In clinical studies, 1 to 2 out of 100 women got pregnant during the first year that they used the norelgestromin and ethinyl estradiol transdermal system.

Norelgestromin and ethinyl estradiol transdermal system may not be as effective in women weighing more than 198 lbs. (90 kg). If you weigh more than 198 lbs. (90 kg), talk to your healthcare provider about which method of birth control is right for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The

most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Do not use norelgestromin and ethinyl estradiol transdermal system if you:

- smoke and are over 35 years old
- have or have had blood clots in your arms, legs, eyes or lungs
- have an inherited problem that makes your blood clot more than normal
- have had a stroke
- have had a heart attack
- have certain heart valve problems or heart rhythm problems that can cause blood clots to form in the heart
- have high blood pressure that medicine cannot control
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headaches if you are over age 35
- have a BMI of 30 or more
- have liver disease, including liver tumors, take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme “alanine aminotransferase” (ALT) in the blood.
- have unexplained vaginal bleeding

- are pregnant or think you may be pregnant. However, norelgestromin and ethinyl estradiol transdermal system is not known to cause birth defects when used by accident during pregnancy.
- have had breast cancer or any cancer that is sensitive to female hormones

Hormonal birth control methods may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy or related to previous use of hormonal birth control.

Tell your healthcare provider if you have ever had any of the above conditions. Your healthcare provider may recommend another method of birth control.

Before you use norelgestromin and ethinyl estradiol transdermal system, tell your healthcare provider:

- about all your medical conditions
- if you are pregnant or think you are pregnant
- if you are scheduled for surgery. Norelgestromin and ethinyl estradiol transdermal system may increase your risk of blood clots after surgery. You should stop using your norelgestromin and ethinyl estradiol transdermal patch at least 4 weeks before you have surgery and not restart it until at least 2 weeks after your surgery.
- if you are scheduled for any laboratory tests. Certain blood tests may be affected by hormonal birth control methods.
- are breastfeeding or plan to breastfeed. Hormonal birth control methods that contain estrogen, like norelgestromin and ethinyl estradiol transdermal system, may decrease the amount of milk you make. A small amount of hormones from the norelgestromin and ethinyl estradiol transdermal patch may pass into your breast milk. Consider another method of birth control until you are ready to stop breastfeeding.

Tell your healthcare provider about all medicines and herbal products that you take.

Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

- certain seizure medicines (carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, and topiramate)
- aprepitant
- barbiturates
- bosentan
- griseofulvin
- certain combinations of HIV medicines (nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
- certain non-nucleoside reverse transcriptase inhibitors (nevirapine)
- rifampin and rifabutin
- St. John's wort

Use another birth control method (such as a condom and spermicide or diaphragm and spermicide) when you take medicines that may make the norelgestromin and ethinyl estradiol transdermal patch less effective.

Some medicines and grapefruit juice may increase your level of the hormone ethinyl estradiol if used together, including:

- acetaminophen
- ascorbic acid

- medicines that affect how your liver breaks down other medicines (itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir, indinavir)
- atorvastatin
- rosuvastatin
- etravirine

Hormonal birth control methods may interact with lamotrigine, an anti-seizure medicine used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use norelgestromin and ethinyl estradiol transdermal system?

- **For detailed instructions, see the step-by-step instructions for using norelgestromin and ethinyl estradiol transdermal system at the end of this Patient Information.**
- Use norelgestromin and ethinyl estradiol transdermal system exactly as your healthcare provider tells you to use it.
- Wear 1 norelgestromin and ethinyl estradiol transdermal patch at a time. Make sure you remove your old norelgestromin and ethinyl estradiol transdermal patch before applying your new norelgestromin and ethinyl estradiol transdermal patch.
- **Do not** skip using any norelgestromin and ethinyl estradiol transdermal patches, even if you do not have sex often.
- Norelgestromin and ethinyl estradiol transdermal system is applied in a 4-week cycle.
 - Apply your norelgestromin and ethinyl estradiol transdermal patch 1 time each week for 3 weeks (21 total days).
 - Apply each new norelgestromin and ethinyl estradiol transdermal patch on the same day of the week. This day will be your "Patch Change Day." For example, if you apply your first norelgestromin and ethinyl estradiol transdermal patch on a Monday, all of your norelgestromin and ethinyl estradiol transdermal patches should be applied on a Monday.
 - **Do not** apply your norelgestromin and ethinyl estradiol transdermal patch during Week 4. Make sure you remove your old norelgestromin and ethinyl estradiol transdermal patch. This is your patch-free week. Your menstrual period should start during your patch-free week.
 - Begin a new 4 week cycle by applying a new norelgestromin and ethinyl estradiol transdermal patch on the day after Week 4 ends. Repeat the cycle of 3 weekly applications followed by a patch-free week.

<i>Calendar</i>						
<i>Sunday</i>	<i>Monday</i>	<i>Tuesday</i>	<i>Wednesday</i>	<i>Thursday</i>	<i>Friday</i>	<i>Saturday</i>
Day 1	Week 1 →					
Day 8	Week 2 →					
Day 15	Week 3 →					
X	Week 4 NO PATCH →					

- Your norelgestromin and ethinyl estradiol transdermal patch should never be off for more than 7 days in a row. If your norelgestromin and ethinyl estradiol transdermal patch is off for more than 7 days in a row and you have sex during this time, you could become pregnant.
- If you miss a period you might be pregnant. Some women miss their periods or have light periods on hormonal birth control methods even when they are not pregnant. Call your healthcare provider if you miss 1 period and have not used your norelgestromin and ethinyl estradiol transdermal patch every day or you miss 2 periods in a row.

What are the possible side effects of norelgestromin and ethinyl estradiol transdermal system?

See "What is the most important information I should know about norelgestromin and ethinyl estradiol transdermal system?"

Norelgestromin and ethinyl estradiol transdermal system may cause serious side effects, including:

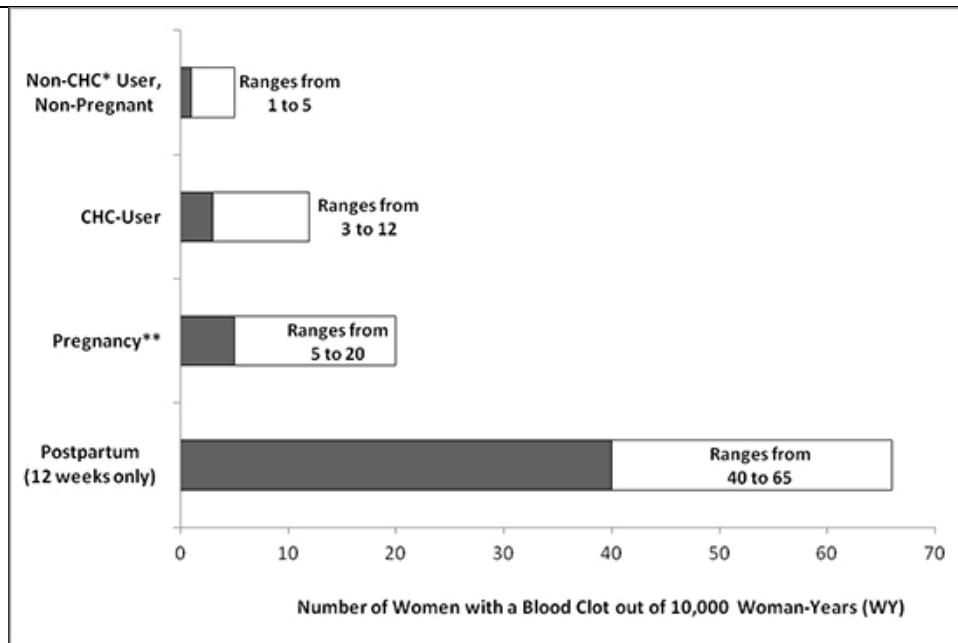
- **blood clots.** Like pregnancy, hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, high blood pressure, high levels of fat in the blood, diabetes, obesity, a family history of blood clots, or age greater than 35. This increased risk is highest when you first start using hormonal birth control and when you restart the same or different hormonal birth control after not using it for a month or more. Some studies have reported that women who use norelgestromin and ethinyl estradiol transdermal system have a higher risk of getting a blood clot. Talk with your healthcare provider about your risk of getting a blood clot before using norelgestromin and ethinyl estradiol transdermal system or deciding which type of birth control is right for you.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- legs (deep vein thrombosis)
- lungs (pulmonary embolus)
- eyes (loss of eyesight)
- heart (heart attack)
- brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use hormonal birth control are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use hormonal birth control, for women who use hormonal birth control, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot (Venous Thromboembolism [VTE])



*CHC=combination hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Call your healthcare provider right away if you have:

- leg pain that will not go away
- sudden shortness of breath
- sudden blindness, partial or complete
- severe pain or pressure in your chest
- sudden, severe headache unlike your usual headaches
- weakness or numbness in an arm or leg, or trouble speaking
- yellowing of the skin or eyeballs

Other serious risks include

- liver problems including liver tumors
- gallbladder disease
- high blood pressure

The most common side effects of norelgestromin and ethinyl estradiol transdermal system are:

- breast symptoms (discomfort, swelling, or pain)
- nausea
- headache
- skin irritation, redness, pain, swelling, itching or rash at the patch application site
- stomach pain
- pain during menstruation
- vaginal bleeding and menstrual disorders, such as spotting or bleeding between periods
- mood, affect and anxiety disorders

Some women have spotting or light bleeding, breast tenderness, or feel sick to their stomach during norelgestromin and ethinyl estradiol transdermal system use. If these symptoms occur, do not stop using the

norelgestromin and ethinyl estradiol transdermal patch. The problem will usually go away. If it does not go away, check with your healthcare provider.

Less common side effects are:

- acne
- less sexual desire
- bloating or fluid retention
- blotchy darkening of your skin, especially your face
- high blood sugar, especially in women with diabetes
- high fat (cholesterol, triglycerides) levels in the blood
- depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- problems tolerating contact lenses
- weight gain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects of norelgestromin and ethinyl estradiol transdermal system. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store and throw away used norelgestromin and ethinyl estradiol transdermal patches?

- Store at room temperature between 59°F to 86°F (15°C to 30°C).
- Do not store norelgestromin and ethinyl estradiol transdermal patches outside of their pouches. Apply immediately upon removal from the protective pouch.
- Do not store in the refrigerator or freezer.
- Used norelgestromin and ethinyl estradiol transdermal patches still contain some active hormones. To throw away the norelgestromin and ethinyl estradiol transdermal patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place this container in the trash. Do not flush used norelgestromin and ethinyl estradiol transdermal patches down the toilet.
- Return unused, unneeded, or expired patches to your pharmacist.

Keep norelgestromin and ethinyl estradiol transdermal system and all medicines out of the reach of children.

General information about the safe and effective use of norelgestromin and ethinyl estradiol transdermal system

Medicines are sometimes prescribed for purposes other than those listed in Patient Information. Do not use norelgestromin and ethinyl estradiol transdermal system for a condition for which it was not prescribed. Do not give norelgestromin and ethinyl estradiol transdermal system to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about norelgestromin and ethinyl estradiol transdermal system that is written for health professionals. For more information, go to www.amneal.com or call 1-877-835-5472.

What are the ingredients in norelgestromin and ethinyl estradiol transdermal system?

Active ingredient: norelgestromin, USP and ethinyl estradiol, USP

Inactive ingredient: pigmented polyethylene and polyester backing, polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol, dipropylene glycol, polyethylene terephthalate (PET) film with a silicone coating.

Do hormonal birth control methods cause cancer?

Hormonal birth control methods do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use hormonal birth control methods because some breast cancers are sensitive to hormones.

Women who use hormonal birth control methods may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What should I know about my period when using norelgestromin and ethinyl estradiol transdermal system?

When you use norelgestromin and ethinyl estradiol transdermal system you may have bleeding and spotting between periods, called unplanned bleeding. Unplanned bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unplanned bleeding occurs most often during the first few months of norelgestromin and ethinyl estradiol transdermal system use, but may also occur after you have been using the patch for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue using the patch on schedule. If the unplanned bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

What if I miss my scheduled period when using norelgestromin and ethinyl estradiol transdermal system?

Some women miss periods on hormonal birth control, even when they are not pregnant. However, if you go 2 or more months in a row without a period, or you miss your period after a month where you did not use all of your patches correctly, or you have symptoms associated with pregnancy, such as morning sickness or unusual breast tenderness, call your healthcare provider because you may be pregnant. Stop taking norelgestromin and ethinyl estradiol transdermal system if you are pregnant.

What if I want to become pregnant?

You may stop using norelgestromin and ethinyl estradiol transdermal system whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop using the patch.

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INSTRUCTIONS FOR USE

Norelgestromin and Ethinyl Estradiol Transdermal System

Norelgestromin and ethinyl estradiol transdermal system is for skin use only.

Do not cut, damage, or alter the norelgestromin and ethinyl estradiol transdermal patch in any way.

How to start using your norelgestromin and ethinyl estradiol transdermal patch:



Figure A

- **If you are not currently using hormonal birth control**, you have 2 ways to begin using your norelgestromin and ethinyl estradiol transdermal patch. Choose the way that is best for you:
 - **First day start:** Apply your first norelgestromin and ethinyl estradiol transdermal patch during the first 24 hours of your menstrual period.
 - **Sunday start:** Apply your first norelgestromin and ethinyl estradiol transdermal patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first norelgestromin and ethinyl estradiol transdermal patch that day, and no back-up birth control is needed.
- **If you are changing from oral hormone birth control pills, a vaginal contraceptive ring or another contraceptive transdermal patch to the norelgestromin and ethinyl estradiol transdermal patch:**
 - Complete your current oral hormone birth control pill cycle, vaginal ring cycle or contraceptive transdermal patch cycle. Apply your first norelgestromin and ethinyl estradiol transdermal patch on the day you would normally start your next oral birth control pill, patch or insert your next vaginal ring.
 - If you do not get your period within 1 week after taking your last active pill, removing your last vaginal ring or contraceptive transdermal patch, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start norelgestromin and ethinyl estradiol transdermal patch for contraception.
 - If you apply your norelgestromin and ethinyl estradiol transdermal patch more than 1 week after taking your last active oral hormone birth control pill, removing your last vaginal ring or contraceptive transdermal patch, use a non-hormonal contraceptive method, such as a condom and spermicide or diaphragm and spermicide, with the norelgestromin and ethinyl estradiol transdermal patch for the first 7 days of patch use.
- **If you are starting norelgestromin and ethinyl estradiol transdermal system after childbirth:**
 - If you are not breastfeeding, wait 4 weeks before using norelgestromin and ethinyl estradiol transdermal system and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your baby was born, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting norelgestromin and ethinyl estradiol transdermal system.

- **If you are starting norelgestromin and ethinyl estradiol transdermal system after a miscarriage or abortion:**
 - You may start norelgestromin and ethinyl estradiol transdermal system immediately after a miscarriage or abortion that occurs in the first 12 weeks (first trimester) of pregnancy. You do not need to use another contraceptive method.
 - If you do not start norelgestromin and ethinyl estradiol transdermal system within 5 days after a first trimester miscarriage or abortion, use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, while you wait for your period to start. You have 2 ways to begin using your norelgestromin and ethinyl estradiol transdermal patch. Choose the way that is best for you:
 - **First day start:** Apply your first norelgestromin and ethinyl estradiol transdermal patch during the first 24 hours of your menstrual period.
 - **Sunday start:** Apply your first norelgestromin and ethinyl estradiol transdermal patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first norelgestromin and ethinyl estradiol transdermal patch that day, and no back-up birth control is needed.
 - If you are starting norelgestromin and ethinyl estradiol transdermal system after a miscarriage or abortion that occurs **after** the first 12 weeks of pregnancy (second trimester), wait 4 weeks before using norelgestromin and ethinyl estradiol transdermal system and use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If you have had sex since your miscarriage or abortion, wait for your first period, or see your healthcare provider to make sure you are not pregnant before starting norelgestromin and ethinyl estradiol transdermal system.

Figure B is a picture of the norelgestromin and ethinyl estradiol transdermal patch.



Figure B

Step 1. Choose a place on your body for your norelgestromin and ethinyl estradiol transdermal patch



- The norelgestromin and ethinyl estradiol transdermal patch may be placed on your upper outer arm, abdomen, buttock or back in a place where it will not be rubbed by tight clothing. Avoid the waistline because clothing and belts may cause your patch to be rubbed off.
- **Do not** apply the patch to your breasts.
- Apply the norelgestromin and ethinyl estradiol transdermal patch only to skin that is clean, dry, and free of any powder, make-up, cream, oil, or lotion.
- Do not apply the norelgestromin and ethinyl estradiol transdermal patch to cut or irritated skin, or in the same location as the previous norelgestromin and ethinyl estradiol transdermal patch.

Step 2: Apply your norelgestromin and ethinyl estradiol transdermal patch

	• Tear open the pouch at the top edge. Peel open the foil pouch that contains the norelgestromin and ethinyl estradiol transdermal patch and its clear plastic cover. Gently remove the norelgestromin and ethinyl estradiol transdermal patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	• Using a fingernail, peel away half of the clear plastic. Avoid touching the sticky surface with your fingers.
	• Apply the sticky side of the norelgestromin and ethinyl estradiol transdermal patch to clean, dry skin. Remove the other half of the clear plastic and apply the entire patch to your skin.
	• Press firmly on the norelgestromin and ethinyl estradiol transdermal patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. • Run your fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the norelgestromin and ethinyl estradiol transdermal patch. • Check your norelgestromin and ethinyl estradiol transdermal patch every day to make sure all edges are sticking correctly.

Step 3: Throwing away your norelgestromin and ethinyl estradiol transdermal patch

- To throw away the norelgestromin and ethinyl estradiol transdermal patch, fold the sticky side of the patch together, place it in a sturdy child-proof container, and place the container in the trash.
- Used norelgestromin and ethinyl estradiol transdermal patches should not be flushed in the toilet.

Important notes:

- **Your norelgestromin and ethinyl estradiol transdermal patch must stick securely to your skin to work properly.**

- **Do not** try to reapply a norelgestromin and ethinyl estradiol transdermal patch if it is no longer sticky, if it has become stuck to itself or another surface, or if it has other material stuck to it. **Do not** tape or wrap the patch to your skin or reapply a patch that is partially adhered to clothing.
- **If your norelgestromin and ethinyl estradiol transdermal patch edge lifts up:**
 - Press down firmly on the patch with the palm of your hand for 10 seconds, making sure that the whole patch sticks to your skin. Run your fingers over the entire surface area to smooth out any “wrinkles” around the edges of the norelgestromin and ethinyl estradiol transdermal patch.
 - If your norelgestromin and ethinyl estradiol transdermal patch does not stick completely, remove it and apply a replacement norelgestromin and ethinyl estradiol transdermal patch.
 - **Do not** tape or wrap the norelgestromin and ethinyl estradiol transdermal patch to your skin or reapply a norelgestromin and ethinyl estradiol transdermal patch that is partially stuck to clothing.
- **If your norelgestromin and ethinyl estradiol transdermal patch has been off or partially off:**
 - **For less than 1 Day**, try to reapply it. If the norelgestromin and ethinyl estradiol transdermal patch does not stick completely, apply a new norelgestromin and ethinyl estradiol transdermal patch immediately. No back-up contraception is needed and your "Patch Change Day" will stay the same.
 - **For more than 1 Day or if you are not sure for how long**, you could become pregnant. To reduce this chance, apply a new norelgestromin and ethinyl estradiol transdermal patch and start a new 4 week cycle. You will now have a new "Patch Change Day." Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first week of your new 4 week norelgestromin and ethinyl estradiol transdermal system cycle.
 - Talk to your healthcare provider about a replacement norelgestromin and ethinyl estradiol transdermal patch prescription so you will always have an extra norelgestromin and ethinyl estradiol transdermal patch available if needed.
- **If you want to move your "Patch Change Day" to a different day of the week**, finish your current cycle. Remove your third norelgestromin and ethinyl estradiol transdermal patch on the correct day.
 - **During week 4**, the "Patch Free Week" (Day 22 through Day 28), you may choose an **earlier** "Patch Change Day" by applying a new patch on the day you prefer. You now have a new Day 1 and a new "Patch Change Day."
- **If your norelgestromin and ethinyl estradiol transdermal patch becomes uncomfortable** or your application site is red, painful or swollen, change your norelgestromin and ethinyl estradiol transdermal patch. Remove your norelgestromin and ethinyl estradiol transdermal patch and apply a new patch to a new location until your next "Patch Change Day."
- **If you forget to change or remove your norelgestromin and ethinyl estradiol transdermal patch:**
 - **At the start of any patch cycle (Week 1, Day 1):**
 - **You could become pregnant. You must use a back-up contraception method for 7 days.** Apply the first norelgestromin and ethinyl estradiol transdermal patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1.
 - **In the middle of your patch cycle (Week 2 or Week 3):**

- **If you forget to change your norelgestromin and ethinyl estradiol transdermal patch for 1 or 2 days**, apply a new norelgestromin and ethinyl estradiol transdermal patch as soon as you remember. Apply your next patch on your normal "Patch Change Day." No back-up contraception method is needed.
 - **If you forget to change your norelgestromin and ethinyl estradiol transdermal patch for more than 2 days**, you could become pregnant. Start a new 4 week cycle as soon as you remember by putting on a new norelgestromin and ethinyl estradiol transdermal patch. You now have a different "Patch Change Day" and a new Day 1. You must use a back-up contraception method for the first 7 days of your new cycle.
- **At the end of your patch cycle (Week 4):**
- **If you forget to remove your norelgestromin and ethinyl estradiol transdermal patch**, take it off as soon as you remember. Start your next cycle on your normal "Patch Change Day," the day after Day 28. No back-up contraception method is needed.
- **If you forget to apply your norelgestromin and ethinyl estradiol transdermal patch at the start of your next patch cycle**, you could become pregnant. Apply the first norelgestromin and ethinyl estradiol transdermal patch of your new cycle as soon as you remember. You now have a new "Patch Change Day" and a new Day 1. Use a non-hormonal back-up contraception method such as a condom and spermicide or diaphragm and spermicide for the first 7 days of your new 4 week norelgestromin and ethinyl estradiol transdermal system cycle.
 - **If you have trouble remembering to change your norelgestromin and ethinyl estradiol transdermal patch**, talk to your healthcare provider about how to make patch changing easier or about using another method of contraception.
 - **If you are not sure how to use your norelgestromin and ethinyl estradiol transdermal patch:**
 - Use a back-up contraception method such as a condom and spermicide or diaphragm and spermicide anytime you have sex. Make sure to have 1 of these non-hormonal contraception methods ready at all times.
 - Talk to your healthcare provider for instructions on using your norelgestromin and ethinyl estradiol transdermal patch.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Distributed by:
Anneal Pharmaceuticals LLC
 Bridgewater, NJ 08807

Rev. 02-2021-00

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

LABELING REVIEW(S)

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	February 17, 2021
ANDA Number(s)	213950
Review Number	4
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	02/16/2021 (response to Labeling DRL)
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion	
☒ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

N/A.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received February 16, 2021.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

N/A

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

- The applicant submitted a point-by-point response to prescribing information (PI), patient information labeling (PIL), and instructions for use (IFU) labeling deficiencies identified in Labeling Review #3-Addendum (C3-Add) based on the 7/28/20 submission. All deficiency comments were addressed.
- As the comments to the applicant per C3-Add were extensive, for brevity, only the applicant's responses will be shown below.

Response to PI comment:

Amneal's Response:

Amneal acknowledges all Agencies' comments and accordingly has revised Prescribing Information as per the comments above. Please refer to **Module 1.14.2.3** for the revised Package Insert ([MS-Word](#), [PDF](#), [SPL](#) and [FPL](#)) and [Module 1.14.3.1](#) for the side-by-side comparison of Amneal's revised Package Insert (Revision: 02-2021-00) versus Amneal's previously submitted Package Insert (Revision: 07-2020-00).

Response to PIL comment:

Amneal's Response:

Amneal acknowledges the Agency's comment and accordingly has revised Patient Information. Please refer to **Module 1.14.2.3** for the revised Patient Information ([MS-Word](#), [PDF](#) and [FPL](#)) and [Module 1.14.3.1](#) for the side-by-side comparison of Amneal's revised Patient Information (Revision: 02-2021-00) versus Amneal's previously submitted Patient Information (Revision: 07-2020-00).

Response to IFU comment:

Amneal's Response:

Amneal acknowledges the Agency's comment and accordingly has revised Instructions for Use. Please refer to **Module 1.14.2.3** for final Instructions for Use ([MS-Word](#), [PDF](#) and [FPL](#)), and [Module 1.14.3.1](#) for side by side labeling comparisons of Amneal's current Instructions for Use (Revision: 02-2021-00) with that of Amneal's previously submitted Instructions for Use (Revision: 07-2020-00).

- The full response letter is attached below:



2-16-21

amend_cover-letter-

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

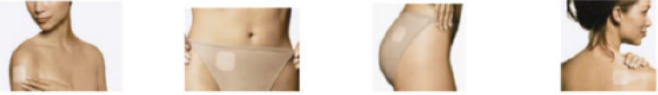
The patch, pouch, carton, and reminder sticker labeling was found satisfactory in C1 and C2 based on the 12/18/19 and 3/25/20 submissions. No new patch, pouch, carton, and reminder sticker labeling were submitted in the 2/16/21 submission.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Per chemistry (R02) review, uploaded 1/28/2021, the following assessments for labeling:

Labeling	
Description	
Is the information accurate?	☒ YES ☐ NO
Is the drug product subject of a USP monograph?	☐ YES ☒ NO
Does the labeling need a special USP statement in the Description?	☐ YES ☒ NO
Comment: N/A	
How Supplied	
Is the information accurate?	☒ YES ☐ NO
Are the storage conditions acceptable?	☒ YES ☐ NO
Dosage and Administration	
Is the schematic in product insert (Section 1.14 Labeling) an accurate representation of the actual product design? CHOOSING A PLACE ON THE BODY TO PUT THE PATCH	☒ YES ☐ NO
	
HOW TO APPLY THE PATCH	

	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	
Not Applicable	
Identifying label present and adequate?	
☒ YES ☐ NO	
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	
☐ YES ☒ NO	
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

Deficiencies –

DS: None

DP: None

Labeling: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP Affecting Multiple Drug Products	FDA 2019-P-2286	Multiple, Hormonal Contraceptives; including Depo Provera, Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) and Progestogen-only contraceptives (POCs)	Multiple: Hormonal Contraceptives; including Depo Provera (Depot Medroxyprogesterone Acetate (DMPA)), Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) and Progestogen-only contraceptives (POCs)	Requests FDA to remove from the market the injectable contraceptive Depot Medroxyprogesterone Acetate (DMPA, Depo Provera)
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead		All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP		If your application is one of these drug products (which include: Ethinyl Estradiol, Levonorgestrel, Norethindrone, Norgestimate, Desogestrel, Progestin, Mestranol, Norgestrel, Drospirenone), please contact Policy Lead to determine if your product is one listed in CP. Contact Policy Lead to upload MTF prior to any approval actions.

The listing from 5/10/19 does not appear to be applicable as the action requested is referring to the injectable contraceptives, the Notes column includes drug products including Ethinyl Estradiol. Thus, this listing is flagged.

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

****NDA 021180 is Withdrawn FR as of 07/12/2018:**

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices 32305

NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.
NDA 021633	Femtrace (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): 200910/S-010 (RS)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISCN	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

Supplement Approval Date: 12/31/2020

Proprietary Name: Xulane

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: The sANDA, submitted as "Prior Approval Supplement," provides for labeling revisions to better assist prescribers and patients with using Xulane.

Per S-010 applicant's cover letter:

Mylan Technologies Inc. wishes to supplement the above-referenced Abbreviated New Drug Application (ANDA) with labeling revisions to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. After approval on April 24, 2020 of Mylan Technologies Inc.'s Prior Approval Supplement (S-008) to incorporate new safety information related to Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) in accordance with Section 505(o)(4) of the FDCA, Mylan re-evaluated the non-data aspects of Xulane's Prescribing Information, Patient Information/Instructions for Use and Patient Information Card (PIC Card). Accordingly, within this supplement, Mylan has proposed labeling content and formatting changes to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. Please note that, as the Reference Listed Drug (RLD) for this product, Ortho Evra[®] (NDA 021180), is currently classified as "Discontinued" in the Agency's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), Mylan is submitting our proposed labeling revisions as a Prior Approval Supplement based on the review process broadly described in the Agency's Guidances, *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016) and *Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

A PDF of the currently approved [Prescribing Information/Patient Information/Instructions for Use](#) is provided in Section 1.14.2.3 and a PDF of the current [Patient Information Card \(PIC Card\)](#) is provided in Section 1.14.2.2 for reference.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

The following CMC supplement was approved after the last approved RS ANDA labeling but had no impact on labeling:

- S-013, approved 2/10/21

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

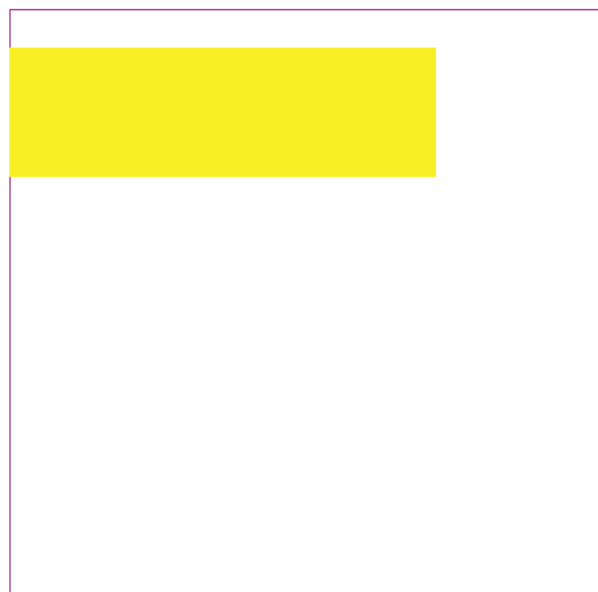
Reviewer Comments:

The applicant made all revisions requested per C3-Addendum.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021180 Annual Report-16, dated 1/16/18]

NDA 021180 AR-14, dated 1/15/16:



Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your calendar.



Place these stickers on your pouches.

ORTHO-McNEIL

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ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08859-0802





3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 2/18/2021.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 2/18/2021.

Table 3 provides Orange Book patents for the Model Labeling NDA 021180 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. <u>The backing layer</u> is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. <u>The middle layer</u> contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN, USP and EE, USP. <u>The third layer is the release liner</u>, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. <u>The backing layer</u> is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. <u>The middle layer</u> contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN, USP and EE, USP. <u>The third layer is the release liner</u>, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	No change.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	No change.

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Anneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Anneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	N/A	03/25/2020	Satisfactory in Labeling Review #2
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory in Labeling Review #1
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	
Reminder Sticker	Final	N/A	12/18/2019	
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Rev. 02-2021-00	12/16/2021	Satisfactory
Patient Information		Rev. 02-2021-00		Satisfactory
Instructions for Use		Rev 02-2021-00		Satisfactory



Alison
Park

Digitally signed by Alison Park
Date: 2/18/2021 01:41:18PM
GUID: 506354110000db251c2d2cd0f7476af



Ellen
Koo

Digitally signed by Ellen Koo
Date: 2/18/2021 03:47:49PM
GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 31, 2020 (February 11, 2021 – ADDENDUM)
ANDA Number(s)	213950
Review Number	3 – ADDENDUM (Addendum comments in BLUE)
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	07/28/2020 (response to labeling DRL)
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion	
☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 12, 2021 based on your submission received July 28, 2020:

1. PRESCRIBING INFORMATION

Revise your labeling to be in accordance with the model labeling, which includes the following revisions below.

a. HIGHLIGHTS OF PRESCRIBING INFORMATION

- i. Revise the following section as such:

----- INDICATIONS AND USAGE -----

Norelgestromin and ethinyl estradiol transdermal system is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women with a BMI < 30 kg/m² for whom a combined hormonal contraceptive is appropriate. (1)

b. FULL PRESCRIBING INFORMATION

- i. **Warning** box: Revise (b) (4) to read, "Events" in the first bullet heading.
- ii. Revise the following section as such:

1 INDICATIONS AND USAGE

Norelgestromin and ethinyl estradiol transdermal system is indicated for the prevention of pregnancy in women with a body mass index (BMI) < 30 kg/m² for whom a combined hormonal contraceptive is appropriate.

- iii. **2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System** subsection: Revise the entire text prior to "**Use after Childbirth**" heading as such:

2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System

There are multiple options for starting the norelgestromin and ethinyl estradiol transdermal system, and the woman should choose the option that is most appropriate (see Table 1):

Table 1: Instructions for Administration

Starting norelgestromin and ethinyl estradiol transdermal system in women with no current use of hormonal contraception
The woman has two options for starting the patch and she should choose the option that is right for her: First Day Start • The woman should apply her first patch during the first 24 hours of her menstrual period. If a patch is applied after the first 24 hours of menstruation, non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) is needed for the first 7 days of the first cycle only. • The woman should apply a new patch each week for three weeks (21 total days). Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. • No patch is worn during Week Four (the "Patch-Free Week"). Withdrawal bleeding is expected during this time.

- On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles. Sunday Start - The woman should apply her first patch on the first Sunday after her menstrual period begins. - With this option, a non-hormonal backup method of birth control, such as a condom and spermicide or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. - If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.	
Switching from another contraceptive method	
Oral combination hormonal contraception (oral CHC)	- If the woman is switching from the pill to norelgestromin and ethinyl estradiol transdermal system, she should complete her current pill cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally start her next pill - If she does not get her period within a week after taking the last active pill, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. - If the patch is applied more than a week after taking the last active pill, she should use a non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.
Transdermal system	- If the woman is switching from another contraceptive transdermal system to norelgestromin and ethinyl estradiol transdermal system, she should complete the current transdermal system cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next transdermal system cycle would normally start. - If she does not get her period within a week after removing the last transdermal system, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. If norelgestromin and ethinyl estradiol transdermal system is applied more than a week after removal of the last patch, nonhormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Vaginal ring	- If the woman is switching from the vaginal ring to norelgestromin and ethinyl estradiol transdermal system, she should complete her current vaginal ring cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally insert her next vaginal ring. - If she does not get her period within a week after removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. - If the patch is applied more than a week after removal of the last vaginal ring, she should use a non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.

Injection	• If the woman is switching from an injection contraceptive to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next injection would normally occur.
Intrauterine system (IUS)	• If the woman is switching from an intrauterine system to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of IUS removal. If the IUS is not removed on the first day of the menstrual cycle, nonhormonal backup contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Implant	• If the woman is switching from an implant to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of implant removal.
Progestin-only pill	• If the woman is switching from a progestin-only pill to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next progestin-only pill cycle would normally start.

- iv. **5.7 Carbohydrate and Lipid Metabolic Effects** subsection, 1st paragraph, 3rd sentence: Add “transdermal system” as such:
In a 6-cycle clinical trial with norelgestromin and ethinyl estradiol transdermal system there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.
- v. **5.9 Bleeding Irregularities** subsection: Renumber all Tables and references to such Tables going forward as a “new” Table 1 was added in subsection 2.2.
- vi. **5.14 Monitoring** subsection: Revise (b) (4) ...” to read, “...should have routine visits with...”.
- vii. **7.1 Effects of Other Drugs on Combined Hormonal Contraceptives** subsection: Bold and Italicize using Title Case the three paragraph headings (e.g., *Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs*:).
- viii. **7.3 and 7.4** subsections: Transpose the heading and text for these two sections to align with your CONTENTS* section (i.e., Correct order is: **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation** and **7.4 Interference with Laboratory Tests**).
- ix. **14 CLINICAL STUDIES** section: Include the dosage form term (i.e., transdermal system) after “norelgestromin and ethinyl estradiol” in five instances throughout this section.

2. PATIENT INFORMATION

What is the most important information I should know about norelgestromin and ethinyl estradiol transdermal system? section, 3rd paragraph: Revise (b) (4) to read “30 kg/m²”.

3. INSTRUCTIONS FOR USE

How to start using your norelgestromin and ethinyl estradiol transdermal patch: section, 2nd solid bullet: Revise the entire bullet and sub-bullets as follows:

- If you are changing from oral hormone birth control pills, a vaginal contraceptive ring or another contraceptive transdermal patch to the norelgestromin and ethinyl estradiol transdermal patch:
 - Complete your current oral hormone birth control pill cycle, vaginal ring cycle or contraceptive transdermal patch cycle. Apply your first norelgestromin and ethinyl estradiol transdermal patch on the day you would normally start your next oral birth control pill, patch or insert your next vaginal ring.
 - If you do not get your period within 1 week after taking your last active pill, removing your last vaginal ring or contraceptive transdermal patch, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start norelgestromin and ethinyl estradiol transdermal patch for contraception.
 - If you apply your norelgestromin and ethinyl estradiol transdermal patch more than 1 week after taking your last active oral hormone birth control pill, removing your last vaginal ring or contraceptive transdermal patch, use a non-hormonal contraceptive method, such as a condom and spermicide or diaphragm and spermicide, with the norelgestromin and ethinyl estradiol transdermal patch for the first 7 days of patch use.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

N/A

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The applicant submitted a response to prescribing information (PI) and patient information labeling (PIL) deficiencies identified in Labeling Review #2 (C2) based on the 3/25/20 submission.

Portion taken from response letter:

Pursuant to 21 C.F.R § 314.96, Amneal Pharmaceuticals LLC ("Amneal") hereby submits the **Discipline Review Letter - Labeling** to ANDA # 213950, Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg, as per the deficiency letter received from the Agency on July 28, 2020 (**See Attached**).

Amneal's Response:

Amneal acknowledges the Agency's comment. Accordingly, Amneal has revised the Prescribing Information and Patient Information sections of the Package Insert to include the labeling updates as requested in this Discipline Review Letter

Please refer to below Modules for revised labeling components:

- Module 1.14.2.3 for Amneal's revised Package Insert (**MS-Word**, **PDF**, **SPL** and **FPL**).
- Module 1.14.2.3 for Amneal's revised Patient Information Insert (**MS-Word**, **PDF**, and **FPL**).
- Module 1.14.2.3 for Amneal's revised Instructions for Use Insert (**MS-Word**, **PDF**, and **FPL**).
- **Module 1.14.3.1** for the annotated comparison of Amneal's proposed Package Insert vs. Amneal's previously submitted Package Insert.



7-28-20

amend_cover-letter-

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

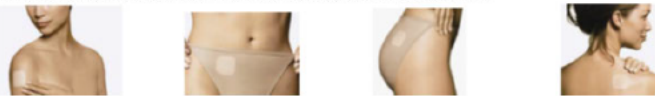
The patch, pouch, carton, and reminder sticker labeling was found satisfactory in C1 and C2 based on the 12/18/19 and 3/25/20 submissions. No new labels were submitted in the 7/28/20 submission.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Per chemistry (R02) review, uploaded 1/28/2021, the following assessments for labeling:

Labeling	
Description	
Is the information accurate?	☒ YES ☐ NO
Is the drug product subject of a USP monograph?	☐ YES ☒ NO
Does the labeling need a special USP statement in the Description?	☐ YES ☒ NO
Comment: N/A	
How Supplied	
Is the information accurate?	☒ YES ☐ NO
Are the storage conditions acceptable?	☒ YES ☐ NO
Dosage and Administration	
Is the schematic in product insert (Section 1.14 Labeling) an accurate representation of the actual product design? CHOOSING A PLACE ON THE BODY TO PUT THE PATCH	
	☒ YES ☐ NO
HOW TO APPLY THE PATCH	
	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Not Applicable
Identifying label present and adequate?	☒ YES ☐ NO
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	☐ YES ☒ NO
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

Deficiencies –
 DS: None
 DP: None
 Labeling: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO
 If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES
 If Yes, please explain.

CP Affecting Multiple Drug Products	FDA 2019-P-2289	Multiple, Hormonal Contraceptives; including Depo Provera, Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal, and transdermal formulations) and Progestogen-only contraceptives (POCs)	Multiple: Hormonal Contraceptives; including Depo Provera (Depot Medroxyprogesterone Acetate (DMPA)), Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) and Progestogen-only contraceptives (POCs)	Requests FDA to remove from the market the injectable contraceptive Depot Medroxyprogesterone Acetate (DMPA; Depo Provera)
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead		All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP		If your application is one of these drug products (which include: Ethinyl Estradiol, Levonorgestrel, Norethindrone, Norgestimate, Desogestrel, Progestin, Mestranol, Norgestrel, Drospirenone), please contact Policy Lead to determine if your product is one listed in CP. Contact Policy Lead to upload MTF prior to any approval actions.

The listing from 5/10/19 does not appear to be applicable as the action requested is referring to the injectable contraceptives, the Notes column includes drug products including Ethinyl Estradiol. Thus, this listing is flagged.

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
 (Check the box used as the Model Labeling)

MOST RECENTLY APPROVED **NDA** MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

**NDA 021180 is Withdrawn FR as of 07/12/2018:

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices		32305
NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.	
NDA 021633	Femtra (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg	

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme

alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): 200910/S-010 (RS)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISCN	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

Supplement Approval Date: 12/31/2020

Proprietary Name: Xulane

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: The sANDA, submitted as "Prior Approval Supplement," provides for labeling revisions to better assist prescribers and patients with using Xulane.

Per S-010 applicant's cover letter:

Mylan Technologies Inc. wishes to supplement the above-referenced Abbreviated New Drug Application (ANDA) with labeling revisions to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. After approval on April 24, 2020 of Mylan Technologies Inc.'s Prior Approval Supplement (S-008) to incorporate new safety information related to Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) in accordance with Section 505(o)(4) of the FDCA, Mylan re-evaluated the non-data aspects of Xulane's Prescribing Information, Patient Information/ Instructions for Use and Patient Information Card (PIC Card). Accordingly, within this supplement, Mylan has proposed labeling content and formatting changes to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. Please note that, as the Reference Listed Drug (RLD) for this product, Ortho Evra[®] (NDA 021180), is currently classified as "Discontinued" in the Agency's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), Mylan is submitting our proposed labeling revisions as a Prior Approval Supplement based on the review process broadly described in the Agency's Guidances, *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016) and *Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

A PDF of the currently approved [Prescribing Information/Patient Information/Instructions for Use](#) is provided in Section 1.14.2.3 and a PDF of the current [Patient Information Card \(PIC Card\)](#) is provided in Section 1.14.2.2 for reference.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

The following CMC supplement was approved after the last approved RS ANDA labeling but had no impact on labeling:

- S-013, approved 2/10/21

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

- The applicant accurately made most of the requested revisions per C2.
- However, the RS ANDA model labeling was recently updated on 12/31/20 (S-010) which supersedes the subject ANDA's 7/28/20 submission. Refer to section 1.1 for detailed deficiency comments to the applicant.
- As noted in the labeling review for RS ANDA 200910/S-010, pending ANDAs referencing the RLD NDA should be updated using the RS ANDA as the model labeling.

Portion taken from RS ANDA 200910/S-010 labeling review:

Note that the following generic applications reference NDA 021180:

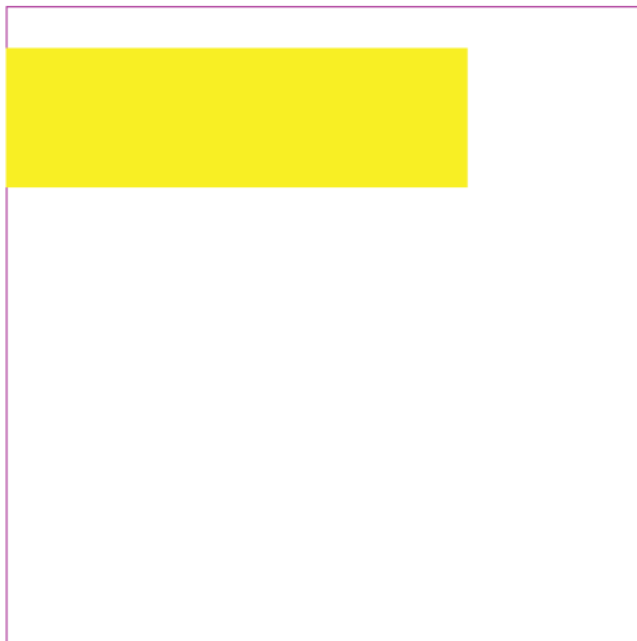
RLD is referenced by	CDER	ANDA-213950	Unknown	Pending	08/28/2020	ethinyl estradiol norelgestromin
RLD is referenced by	CDER	ANDA-213977	Unknown	Pending	12/17/2019	Ethinyl Estradiol
(b) (4)						
RLD is referenced by	CDER	ANDA-214594	Unknown	Pending	09/30/2020	Ethinyl Estradiol and Norelgestromin
(b) (4)						

The labeling for the currently pending ANDAs highlighted above, should be updated to be in line with the changes made to the labeling for the subject ANDA once approved. Based on the information documented in the labeling reviews for these ANDAs related to the RS (the subject ANDA), the labeling reviewers appear to be informed about the pending S-010.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: : NDA 021180 Annual Report-16, dated 1/16/18]

NDA 021180 AR-14, dated 1/15/16:



Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your calendar.



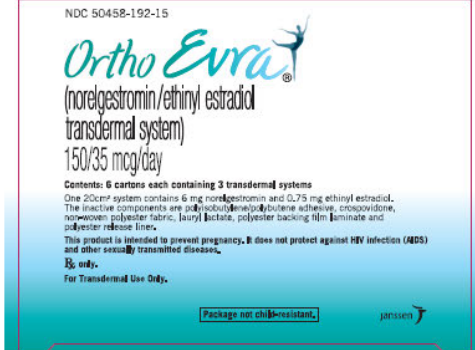
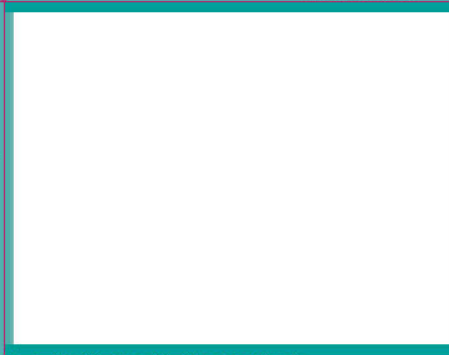
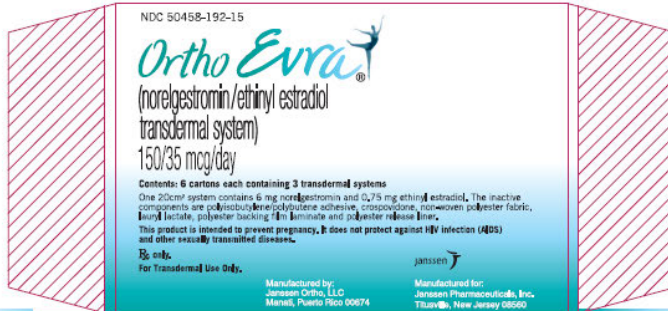
Place these stickers on your pouches.

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ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869-0802

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3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 7/31/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/31/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 021180 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer	Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer	No change.

are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	No change.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	N/A	03/25/2020	Satisfactory in Labeling Review #2
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory in Labeling Review #1
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	
Reminder Sticker	Final	N/A	12/18/2019	

Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Rev. 07-2020-00	07/28/2020	Revise
Patient Information		Rev. 07-2020-00		Revise
Instructions for Use		Rev. 07-2020-00		Revise



Alison
Park

Digitally signed by Alison Park
Date: 2/12/2021 03:43:22PM
GUID: 506354110000db251c2d2cd0f7476af



Ellen
Koo

Digitally signed by Ellen Koo
Date: 2/12/2021 03:45:13PM
GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 31, 2020 (February 11, 2021 – ADDENDUM)
ANDA Number(s)	213950
Review Number	3 – ADDENDUM (Addendum comments in BLUE)
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	07/28/2020 (response to labeling DRL)
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion	
☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on February 12, 2021 based on your submission received July 28, 2020:

1. PRESCRIBING INFORMATION

Revise your labeling to be in accordance with the most recently approved reference standard (RS) labeling, Xulane® ANDA 200910/S-010, approved on December 31, 2020, which includes the following revisions below.

a. HIGHLIGHTS OF PRESCRIBING INFORMATION

- i. Revise the following section as such:

----- INDICATIONS AND USAGE -----

Norelgestromin and ethinyl estradiol transdermal system is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women with a BMI < 30 kg/m² for whom a combined hormonal contraceptive is appropriate. (1)

b. FULL PRESCRIBING INFORMATION

- i. **Warning** box: Revise (b) (4) to read, “Events” in the first bullet heading.
ii. Revise the following section as such:

1 INDICATIONS AND USAGE

Norelgestromin and ethinyl estradiol transdermal system is indicated for the prevention of pregnancy in women with a body mass index (BMI) < 30 kg/m² for whom a combined hormonal contraceptive is appropriate.

- iii. **2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System** subsection: Revise the entire text prior to “*Use after Childbirth*” heading as such:

2.2 How to Start Using Norelgestromin and Ethinyl Estradiol Transdermal System

There are multiple options for starting the norelgestromin and ethinyl estradiol transdermal system, and the woman should choose the option that is most appropriate (see Table 1):

Table 1: Instructions for Administration

Starting norelgestromin and ethinyl estradiol transdermal system in women with no current use of hormonal contraception
The woman has two options for starting the patch and she should choose the option that is right for her: First Day Start - The woman should apply her first patch during the first 24 hours of her menstrual period. If a patch is applied after the first 24 hours of menstruation, non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) is needed for the first 7 days of the first cycle only. - The woman should apply a new patch each week for three weeks (21 total days). Every new patch should be applied on the same day of the week. This day is known as the “Patch Change Day.” For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. - No patch is worn during Week Four (the “Patch-Free Week”). Withdrawal bleeding is expected during this time.

- On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles. Sunday Start - The woman should apply her first patch on the first Sunday after her menstrual period begins. - With this option, a non-hormonal backup method of birth control, such as a condom and spermicide or diaphragm and spermicide, is needed for the first 7 days of the first cycle only. - If her period starts on a Sunday, the first patch should be applied that day, and no backup contraception is needed.	
Switching from another contraceptive method	
Oral combination hormonal contraception (oral CHC)	- If the woman is switching from the pill to norelgestromin and ethinyl estradiol transdermal system, she should complete her current pill cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally start her next pill - If she does not get her period within a week after taking the last active pill, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. - If the patch is applied more than a week after taking the last active pill, she should use a non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.
Transdermal system	- If the woman is switching from another contraceptive transdermal system to norelgestromin and ethinyl estradiol transdermal system, she should complete the current transdermal system cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next transdermal system cycle would normally start. - If she does not get her period within a week after removing the last transdermal system, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. If norelgestromin and ethinyl estradiol transdermal system is applied more than a week after removal of the last patch, nonhormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Vaginal ring	- If the woman is switching from the vaginal ring to norelgestromin and ethinyl estradiol transdermal system, she should complete her current vaginal ring cycle and apply the first norelgestromin and ethinyl estradiol transdermal system on the day she would normally insert her next vaginal ring. - If she does not get her period within a week after removing the last vaginal ring, she should check with her healthcare professional to be sure that she is not pregnant, but she may go ahead and start norelgestromin and ethinyl estradiol transdermal system for contraception. - If the patch is applied more than a week after removal of the last vaginal ring, she should use a non-hormonal back-up contraception (such as condoms and spermicide, or diaphragm and spermicide) concurrently for the first 7 days of patch use.

Injection	• If the woman is switching from an injection contraceptive to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next injection would normally occur.
Intrauterine system (IUS)	• If the woman is switching from an intrauterine system to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of IUS removal. If the IUS is not removed on the first day of the menstrual cycle, nonhormonal backup contraception (such as condoms and spermicide, or diaphragm and spermicide) should be used concurrently for the first 7 days of patch use.
Implant	• If the woman is switching from an implant to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day of implant removal.
Progestin-only pill	• If the woman is switching from a progestin-only pill to norelgestromin and ethinyl estradiol transdermal system, she should apply the first norelgestromin and ethinyl estradiol transdermal system on the day the next progestin-only pill cycle would normally start.

- iv. **5.7 Carbohydrate and Lipid Metabolic Effects** subsection, 1st paragraph, 3rd sentence: Add “transdermal system” as such:

In a 6-cycle clinical trial with norelgestromin and ethinyl estradiol transdermal system there were no clinically significant changes in fasting blood glucose from baseline to end of treatment.
- v. **5.9 Bleeding Irregularities** subsection: Renumber all Tables and references to such Tables going forward as a “new” Table 1 was added in subsection 2.2.
- vi. **5.14 Monitoring** subsection: Revise (b) (4) ...” to read, “...should have routine visits with...”.
- vii. **7.1 Effects of Other Drugs on Combined Hormonal Contraceptives** subsection: Bold and Italicize using Title Case the three paragraph headings (e.g., ***Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs:***).
- viii. **7.3 and 7.4** subsections: Transpose the heading and text for these two sections to align with your CONTENTS* section (i.e., Correct order is: **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation** and **7.4 Interference with Laboratory Tests**).
- ix. **14 CLINICAL STUDIES** section: Include the dosage form term (i.e., transdermal system) after “norelgestromin and ethinyl estradiol” in five instances throughout this section.

2. PATIENT INFORMATION

What is the most important information I should know about norelgestromin and ethinyl estradiol transdermal system? section, 3rd paragraph: Revise (b) (4) to read “30 kg/m²”.

3. INSTRUCTIONS FOR USE

How to start using your norelgestromin and ethinyl estradiol transdermal patch: section, 2nd solid bullet: Revise the entire bullet and sub-bullets as follows:

- If you are changing from oral hormone birth control pills, a vaginal contraceptive ring or another contraceptive transdermal patch to the norelgestromin and ethinyl estradiol transdermal patch:
 - Complete your current oral hormone birth control pill cycle, vaginal ring cycle or contraceptive transdermal patch cycle. Apply your first norelgestromin and ethinyl estradiol transdermal patch on the day you would normally start your next oral birth control pill, patch or insert your next vaginal ring.
 - If you do not get your period within 1 week after taking your last active pill, removing your last vaginal ring or contraceptive transdermal patch, check with your healthcare provider to make sure you are not pregnant. You may still go ahead and start norelgestromin and ethinyl estradiol transdermal patch for contraception.
 - If you apply your norelgestromin and ethinyl estradiol transdermal patch more than 1 week after taking your last active oral hormone birth control pill, removing your last vaginal ring or contraceptive transdermal patch, use a non-hormonal contraceptive method, such as a condom and spermicide or diaphragm and spermicide, with the norelgestromin and ethinyl estradiol transdermal patch for the first 7 days of patch use.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

N/A

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The applicant submitted a response to prescribing information (PI) and patient information labeling (PIL) deficiencies identified in Labeling Review #2 (C2) based on the 3/25/20 submission.

Portion taken from response letter:

Pursuant to 21 C.F.R § 314.96, Amneal Pharmaceuticals LLC ("Amneal") hereby submits the **Discipline Review Letter - Labeling** to ANDA # 213950, Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg, as per the deficiency letter received from the Agency on July 28, 2020 (**See Attached**).

Amneal's Response:

Amneal acknowledges the Agency's comment. Accordingly, Amneal has revised the Prescribing Information and Patient Information sections of the Package Insert to include the labeling updates as requested in this Discipline Review Letter

Please refer to below Modules for revised labeling components:

- Module 1.14.2.3 for Amneal's revised Package Insert (**MS-Word**, **PDF**, **SPL** and **FPL**).
- Module 1.14.2.3 for Amneal's revised Patient Information Insert (**MS-Word**, **PDF**, and **FPL**).
- Module 1.14.2.3 for Amneal's revised Instructions for Use Insert (**MS-Word**, **PDF**, and **FPL**).
- **Module 1.14.3.1** for the annotated comparison of Amneal's proposed Package Insert vs. Amneal's previously submitted Package Insert.



7-28-20

amend_cover-letter-

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

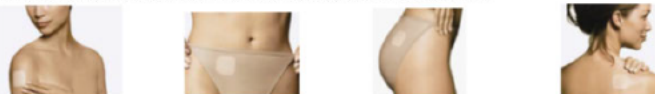
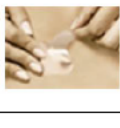
The patch, pouch, carton, and reminder sticker labeling was found satisfactory in C1 and C2 based on the 12/18/19 and 3/25/20 submissions. No new labels were submitted in the 7/28/20 submission.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Per chemistry (R02) review, uploaded 1/28/2021, the following assessments for labeling:

Labeling	
Description	
Is the information accurate?	☒ YES ☐ NO
Is the drug product subject of a USP monograph?	☐ YES ☒ NO
Does the labeling need a special USP statement in the Description?	☐ YES ☒ NO
Comment: N/A	
How Supplied	
Is the information accurate?	☒ YES ☐ NO
Are the storage conditions acceptable?	☒ YES ☐ NO
Dosage and Administration	
Is the schematic in product insert (Section 1.14 Labeling) an accurate representation of the actual product design? CHOOSING A PLACE ON THE BODY TO PUT THE PATCH	☒ YES ☐ NO
	
HOW TO APPLY THE PATCH	
	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Not Applicable
Identifying label present and adequate?	☒ YES ☐ NO
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	☐ YES ☒ NO
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

Deficiencies –
 DS: None
 DP: None
 Labeling: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP Affecting Multiple Drug Products	FDA 2019-P-2289	Multiple, Hormonal Contraceptives; including Depo Provera, Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal, and transdermal formulations) and Progestogen-only contraceptives (POCs)	Multiple: Hormonal Contraceptives; including Depo Provera (Depot Medroxyprogesterone Acetate (DMPA)), Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) and Progestogen-only contraceptives (POCs)	Requests FDA to remove from the market the injectable contraceptive Depot Medroxyprogesterone Acetate (DMPA; Depo Provera)
No Approval Actions (AP/TA) can be taken prior to contacting Policy Lead		All disciplines can continue communications (CRL, IR/DRL); CC should contact Policy if related to CP		If your application is one of these drug products (which include: Ethinyl Estradiol, Levonorgestrel, Norethindrone, Norgestimate, Desogestrel, Progestin, Mestranol, Norgestrel, Drospirenone), please contact Policy Lead to determine if your product is one listed in CP. Contact Policy Lead to upload MTF prior to any approval actions.

The listing from 5/10/19 does not appear to be applicable as the action requested is referring to the injectable contraceptives, the Notes column includes drug products including Ethinyl Estradiol. Thus, this listing is flagged.

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
 (Check the box used as the Model Labeling)

MOST RECENTLY APPROVED **NDA** MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

****NDA 021180 is Withdrawn FR as of 07/12/2018:**

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices		32305
NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.	
NDA 021633	Femtra (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg	

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme

alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): 200910/S-010 (RS)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISCN	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

Supplement Approval Date: 12/31/2020

Proprietary Name: Xulane

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: The sANDA, submitted as "Prior Approval Supplement," provides for labeling revisions to better assist prescribers and patients with using Xulane.

Per S-010 applicant's cover letter:

Mylan Technologies Inc. wishes to supplement the above-referenced Abbreviated New Drug Application (ANDA) with labeling revisions to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. After approval on April 24, 2020 of Mylan Technologies Inc.'s Prior Approval Supplement (S-008) to incorporate new safety information related to Xulane® (norelgestromin and ethinyl estradiol transdermal system) in accordance with Section 505(o)(4) of the FDCA, Mylan re-evaluated the non-data aspects of Xulane's Prescribing Information, Patient Information/ Instructions for Use and Patient Information Card (PIC Card). Accordingly, within this supplement, Mylan has proposed labeling content and formatting changes to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. Please note that, as the Reference Listed Drug (RLD) for this product, Ortho Evra® (NDA 021180), is currently classified as "Discontinued" in the Agency's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), Mylan is submitting our proposed labeling revisions as a Prior Approval Supplement based on the review process broadly described in the Agency's Guidances, *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016) and *Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

A PDF of the currently approved [Prescribing Information/Patient Information/Instructions for Use](#) is provided in Section 1.14.2.3 and a PDF of the current [Patient Information Card \(PIC Card\)](#) is provided in Section 1.14.2.2 for reference.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

The following CMC supplement was approved after the last approved RS ANDA labeling but had no impact on labeling:

- S-013, approved 2/10/21

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

- The applicant accurately made most of the requested revisions per C2.
- However, the RS ANDA model labeling was recently updated on 12/31/20 (S-010) which supersedes the subject ANDA's 7/28/20 submission. Refer to section 1.1 for detailed deficiency comments to the applicant.
- As noted in the labeling review for RS ANDA 200910/S-010, pending ANDAs referencing the RLD NDA should be updated using the RS ANDA as the model labeling.

Portion taken from RS ANDA 200910/S-010 labeling review:

Note that the following generic applications reference NDA 021180:

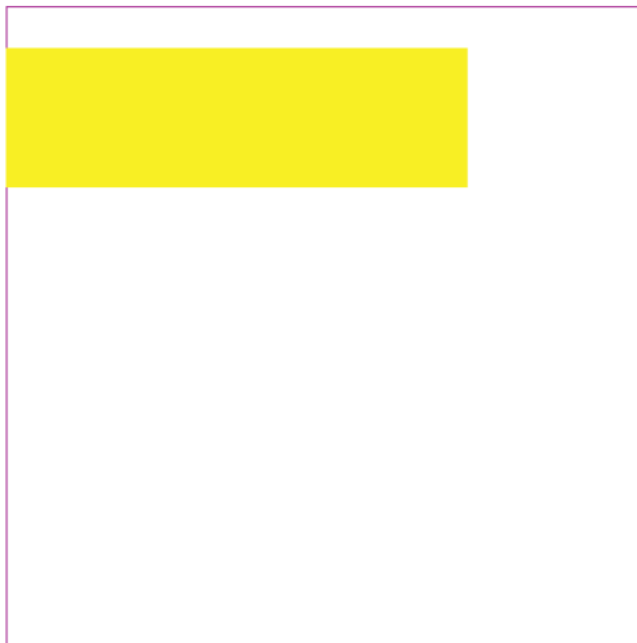
RLD is referenced by	CDER	ANDA-213950	Unknown	Pending	08/28/2020	ethinyl estradiol norelgestromin
RLD is referenced by	CDER	ANDA-213977	Unknown	Pending	12/17/2019	Ethinyl Estradiol
(b) (4)						
RLD is referenced by	CDER	ANDA-214594	Unknown	Pending	09/30/2020	Ethinyl Estradiol and Norelgestromin
(b) (4)						

The labeling for the currently pending ANDAs highlighted above, should be updated to be in line with the changes made to the labeling for the subject ANDA once approved. Based on the information documented in the labeling reviews for these ANDAs related to the RS (the subject ANDA), the labeling reviewers appear to be informed about the pending S-010.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: : NDA 021180 Annual Report-16, dated 1/16/18]

NDA 021180 AR-14, dated 1/15/16:



Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your calendar.



Place these stickers on your pouches.

ORTHO-McNEIL

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ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869-0802





3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 7/31/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/31/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 021180 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer	Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer	No change.

are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	No change.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	N/A	03/25/2020	Satisfactory in Labeling Review #2
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory in Labeling Review #1
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	
Reminder Sticker	Final	N/A	12/18/2019	

Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Rev. 07-2020-00	07/28/2020	Revise
Patient Information		Rev. 07-2020-00		Revise
Instructions for Use		Rev. 07-2020-00		Revise



Alison
Park

Digitally signed by Alison Park
Date: 2/12/2021 01:30:51PM
GUID: 506354110000db251c2d2cd0f7476af



Ellen
Koo

Digitally signed by Ellen Koo
Date: 2/12/2021 03:09:13PM
GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	July 31, 2020
ANDA Number(s)	213950
Review Number	3
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	07/28/2020 (response to labeling DRL)
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☐ ACCEPTABLE – No Comments ☒ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency[†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†]Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☐ Yes ☒ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

N/A.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received July 28, 2020.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

PRESCRIBING INFORMATION

Full Prescribing Information section

- a. Boxed warning, 1st bullet: Revise (b) (4) to ‘Events’.
- b. **5.1 Thromboembolic Disorders and Other Vascular Conditions, Venous Events** heading, 2nd paragraph, 1st sentence: Revise (b) (4) to read, “While the increased risk of VTE...”.
- c. 7.3 and 7.4 subsections: Transpose the heading and text for these two sections to align with your CONTENTS* section (i.e., **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation** and **7.4 Interference with Laboratory Tests**).

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The applicant submitted a response to prescribing information (PI) and patient information labeling (PIL) deficiencies identified in Labeling Review #2 (C2) based on the 3/25/20 submission.

Portion taken from response letter:

Pursuant to 21 C.F.R § 314.96, Amneal Pharmaceuticals LLC ("Amneal") hereby submits the **Discipline Review Letter - Labeling** to ANDA # 213950, Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg, as per the deficiency letter received from the Agency on July 28, 2020 (**See Attached**).

Amneal's Response:

Amneal acknowledges the Agency's comment. Accordingly, Amneal has revised the Prescribing Information and Patient Information sections of the Package Insert to include the labeling updates as requested in this Discipline Review Letter

Please refer to below Modules for revised labeling components:

- Module 1.14.2.3 for Amneal's revised Package Insert (**MS-Word**, **PDF**, **SPL** and **FPL**).
- Module 1.14.2.3 for Amneal's revised Patient Information Insert (**MS-Word**, **PDF**, and **FPL**).
- Module 1.14.2.3 for Amneal's revised Instructions for Use Insert (**MS-Word**, **PDF**, and **FPL**).
- **Module 1.14.3.1** for the annotated comparison of Amneal's proposed Package Insert vs. Amneal's previously submitted Package Insert.



7-28-20

amend_cover-letter-

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?

NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

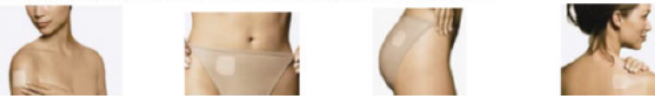
The patch, pouch, carton, and reminder sticker labeling was found satisfactory in C1 and C2 based on the 12/18/19 and 3/25/20 submissions. No new labels were submitted in the 7/28/20 submission.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Per chemistry (R01) review, uploaded 7/30/20, the following assessments for labeling:

Labeling	
Description	
Is the information accurate?	☒ YES ☐ NO
Is the drug product subject of a USP monograph?	☐ YES ☒ NO
Does the labeling need a special USP statement in the Description?	☐ YES ☒ NO
Comment: N/A	
How Supplied	
Is the information accurate?	☒ YES ☐ NO
Are the storage conditions acceptable?	☒ YES ☐ NO
Dosage and Administration	
Is the schematic in product insert (Section 1.14 Labeling) an accurate representation of the actual product design? CHOOSING A PLACE ON THE BODY TO PUT THE PATCH	
	☒ YES ☐ NO
HOW TO APPLY THE PATCH	
	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Not Applicable
Identifying label present and adequate?	☒ YES ☐ NO
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	☐ YES ☒ NO
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

Deficiencies –
DS: None
DP: None
Labeling: None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? NO

If Yes, please explain.

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

****NDA 021180 is Withdrawn FR as of 07/12/2018:**

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices

32305

NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.
NDA 021633	Femtrace (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): 200910/S-008 (RS)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR, 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISCN	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR, 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

Supplement Approval Date: 04/24/2020

Proprietary Name: Xulane

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental abbreviated new drug application provides for revisions to the labeling for Xulane and the agreed upon changes to the language included in the Agency's electronic communication dated March 30, 2020. It also refers to the Agency's letter dated January 23, 2020, notifying the applicant, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for transdermal (TDS) contraceptive products. This information pertains to the risk of venous thromboembolic events (VTE) in obese women.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

The following labeling supplement is PENDING for the RS ANDA 200910:

- **S-010, pending 7/30/20 (goal date 1/30/21):**

Mylan Technologies Inc. wishes to supplement the above-referenced Abbreviated New Drug Application (ANDA) with labeling revisions to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. After approval on April 24, 2020 of Mylan Technologies Inc.'s Prior Approval Supplement (S-008) to incorporate new safety information related to Xulane® (norelgestromin and ethinyl estradiol transdermal system) in accordance with Section 505(o)(4) of the FDCA, Mylan re-evaluated the non-data aspects of Xulane's Prescribing Information, Patient Information/Instructions for Use and Patient Information Card (PIC Card). Accordingly, within this supplement, Mylan has proposed labeling content and formatting changes to better assist prescribers and patients when evaluating this combined hormonal contraceptive transdermal product. Please note that, as the Reference Listed Drug (RLD) for this product, Ortho Evra® (NDA 021180), is currently classified as "Discontinued" in the Agency's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), Mylan is submitting our proposed labeling revisions as a Prior Approval Supplement based on the review process broadly described in the Agency's Guidances, *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016) and *Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

A PDF of the currently approved [Prescribing Information/Patient Information/Instructions for Use](#) is provided in Section 1.14.2.3 and a PDF of the current [Patient Information Card \(PIC Card\)](#) is provided in Section 1.14.2.2 for reference.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **YES**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

The applicant accurately made most of the requested revisions per C2. However, the following minor revisions should be made post approval:

- a. Full Prescribing Information section
 - i. Boxed warning, 1st bullet: Revise (b) (4) to ‘Events’.
 - ii. **5.1 Thromboembolic Disorders and Other Vascular Conditions**, Venous Events heading, 2nd paragraph, 1st sentence: Revise (b) (4) to read, “While the increased risk of VTE...”.
 - iii. 7.3 and 7.4 subsections: Transpose the heading and text for these two sections to align with your CONTENTS* section (i.e., **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation** and **7.4 Interference with Laboratory Tests**).

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: : NDA 021180 Annual Report-16, dated 1/16/18]

NDA 021180 AR-14, dated 1/15/16:



NDC 50458-192-15



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems
One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only.
For Transdermal Use Only.

 Janssen

Manufactured by:
Janssen Ortho, LLC
Merrill, Puerto Rico 00674

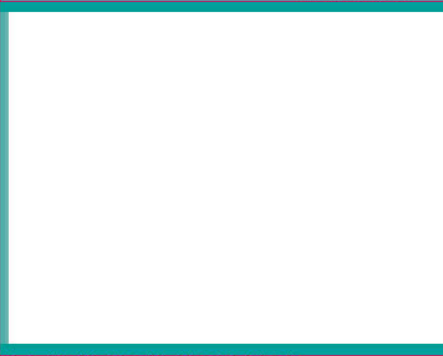
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day



50458-192-15 5



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10211803



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Do Not Remove

 Janssen

excursions permitted to 15 to 30°C (59 to 86°F).
Do not store unopened. Store at 25°C (77°F).
Keep out of reach of children.

IMPORTANT: Each carton contains Detailed Patient Labeling. This should be included with each carton dispensed to the patient.
See package insert.

Each transdermal system is intended to be worn 7 days as prescribed.
150/35 mcg/day
(norelgestromin/ethinyl estradiol
transdermal system)



NDC 50458-192-15

NDC 50458-192-15



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems
One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only.
For Transdermal Use Only.

 Janssen

Package not child-resistant.



3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 7/31/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/31/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 021180 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, NGMN, USP and EE, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.	No change.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.	No change.

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	No change.

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	N/A	03/25/2020	Satisfactory in Labeling Review #2
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory in Labeling Review #1
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	
Reminder Sticker	Final	N/A	12/18/2019	
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Rev. 07-2020-00	07/28/2020	Satisfactory*
Patient Information		Rev. 07-2020-00		Satisfactory
Instructions for Use		Rev. 07-2020-00		Satisfactory
SPL Data Elements		Revised: 7/2020		Satisfactory
*Post approval comment				



Alison
Park

Digitally signed by Alison Park
Date: 7/31/2020 04:26:55PM
GUID: 506354110000db251c2d2cd0f7476af



Lisa
Kwok

Digitally signed by Lisa Kwok
Date: 7/31/2020 05:37:54PM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	June 15, 2020
ANDA Number(s)	213950
Review Number	2
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	03/25/2020 (response to Quality IR)
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion	
☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item.	
*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☐ Yes ☒ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on June 17, 2020 based on your submission received March 25, 2020:

1. PRESCRIBING INFORMATION

Revise your labeling to be in accordance with the most recently approved reference standard (RS) labeling, Xulane® ANDA 200910/S-008, approved on April 24, 2020, which includes the following revisions below.

a. HIGHLIGHTS OF PRESCRIBING INFORMATION

i. **Warning** box: Revise as such:

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI $\geq$ 30 kg/m²

See full prescribing information for complete boxed warning.

- Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women over 35 years old who smoke. Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (4, 5.1)
- Norelgestromin and ethinyl estradiol transdermal system is contraindicated for use in women with a BMI $\geq$ 30 kg/m². Women with a BMI $\geq$ 30 kg/m² who use norelgestromin and ethinyl estradiol transdermal system may have a higher risk of venous thromboembolic events compared with women with a lower BMI. (4, 5.1, 8.8)

- ii. Add the following section heading and text after the boxed warning. *Additionally, for each recent major change listed below in Highlights, the corresponding new or modified text in the Full Prescribing Information must be marked with a vertical line on the left edge.*

----- RECENT MAJOR CHANGES -----

Boxed Warning	4/2020
Indications and Usage (1)	4/2020
Contraindications (4)	4/2020
Warnings and Precautions (5.1)	4/2020
Warnings and Precautions (5.2)	4/2020

- iii. Revise the following section as such:

----- INDICATIONS AND USAGE -----

Norelgestromin and ethinyl estradiol transdermal system is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women with a BMI < 30 kg/m² for whom a transdermal delivery system is an appropriate method of contraception. (1)

Limitations of Use:

Norelgestromin and ethinyl estradiol transdermal system may be less effective in preventing pregnancy in women at or above 198 lbs. (90 kg). (1, 4, 14)

- iv. Revise the following section as such:

----- CONTRAINDICATIONS -----

At high risk of arterial or venous thromboembolic events (4)

- BMI ≥ 30 kg/m² (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

- v. **WARNINGS AND PRECAUTIONS** section: Revise the 1st bullet of this section as such:

- Vascular risks: Stop norelgestromin and ethinyl estradiol transdermal system if a thrombotic event occurs. Stop 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. (5.1)

b. CONTENTS*

- i. Revise the **WARNING** statement as such:

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI ≥ 30 kg/m²

- ii. 5.1: Revise (b) (4) to read, "Conditions".
 iii. 8.8: Revise to read, "BMI and Weight Considerations".
 iv. Delete (b) (4)".

c. FULL PRESCRIBING INFORMATION

- i. **Warning** box: Revise as such:

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS and CONTRAINDICATED IN WOMEN WITH A BMI ≥ 30 kg/m²

- Cigarette Smoking and Serious Cardiovascular Events

Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive 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 norelgestromin and ethinyl estradiol transdermal system, are contraindicated in women who are over 35 years of age and smoke [see *Contraindications (4) and Warnings and Precautions (5.1)*].

- Contraindicated in Women with a BMI ≥ 30 kg/m²

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with a BMI ≥ 30 kg/m². The risk of VTE may be greater with norelgestromin and ethinyl estradiol transdermal system in women with a BMI > 30 kg/m² compared to women with a lower BMI. [see *Contraindications (4) and Warnings and Precautions (5.1)*].

ii. Revise the following section as such:

1 INDICATIONS AND USAGE

Norelgestromin and ethinyl estradiol transdermal system is indicated for the prevention of pregnancy in women with a body mass index (BMI) < 30 kg/m² for whom a transdermal delivery system is an appropriate method of contraception.

Limitations of Use:

Norelgestromin and ethinyl estradiol transdermal system may be less effective in preventing pregnancy in women who weigh 198 lbs. (90 kg) or more.

Norelgestromin and ethinyl estradiol transdermal system is contraindicated for use in women with BMI ≥ 30 kg/m² [see *Contraindications (4), Warnings and Precautions (5.1) and Clinical Studies (14)*].

iii. **4 CONTRAINDICATIONS** section:

1) Revise the first sentence and main bullet as such:

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with the following conditions:

- At high risk of arterial or venous thromboembolic events. Examples include women who:

2) Add the following main bullet (place before the bullet "Liver tumors..."):

- Body Mass Index ≥ 30 kg/m² [see *Warnings and Precautions (5.1)*]

iv. Revise the entire 5.1 and 5.2 sections as such:

5.1 Thromboembolic Disorders and Other Vascular Conditions

- Stop norelgestromin and ethinyl estradiol transdermal system if an arterial or venous thromboembolic event (VTE) occurs.
- Stop norelgestromin and ethinyl estradiol transdermal system if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- If feasible, stop norelgestromin and ethinyl estradiol transdermal system at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE. Discontinue use of norelgestromin and ethinyl estradiol transdermal system during prolonged immobilization and resume treatment based on clinical judgment.
- Start norelgestromin and ethinyl estradiol transdermal system no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

- Before starting norelgestromin and ethinyl estradiol transdermal system, evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. [see *Contraindications (4)*].

Arterial Events

The use of CHCs increases the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and women with hypertension, dyslipidemia, diabetes, or obesity. Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women over 35 years of age who smoke [see *Contraindications (4)*]. Cigarette smoking increases the risk of serious cardiovascular events from CHC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

Venous Events

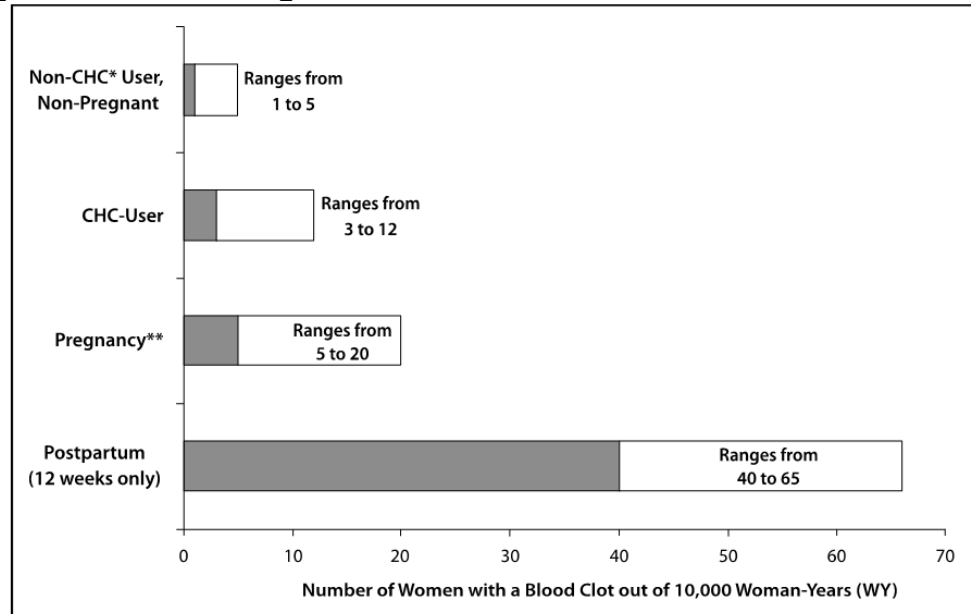
The use of CHCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs. The risk of VTE may be greater with norelgestromin and ethinyl estradiol transdermal system in women with a BMI $\geq$ 30 kg/m² compared to women with a lower BMI [see *Contraindications (4)*].

While the increased risk of VTE associated with use of CHCs is well-established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The frequency of VTE in women using CHCs has been estimated to be 3 to 12 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of CHCs and when restarting hormonal contraception after a break of 4 weeks or longer. This initial higher risk declines during the first year, but users of CHCs remain at an increased risk of VTE compared to non-users of CHCs. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued.

Figure 1 shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs with a range of doses and routes of administration, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use CHCs are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 1: Likelihood of Developing a VTE Within One Year Among Pregnant and Non-Pregnant Women



* CHC = combination hormonal contraception

** Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is 9 months, the incidence rate is 7 to 27 per 10,000 women-years.

5.2 Ethinyl Estradiol Exposure

Higher estrogen exposure may increase the risk of adverse reactions, including venous thromboembolism (VTE). The Area Under the Curve (AUC) for ethinyl estradiol (EE) is approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared to oral contraceptives containing EE 35 mcg. In contrast, the peak concentration (C_{max}) for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system [see *Clinical Pharmacology (12.3)*].

- v. Going forward, ensure that your Table and Figure numbers (and all references to such Tables and Figures) is one digit below the original number (i.e., “Table 2” should now be called “Table 1”, etc.).
- vi. Revise the subsection heading and text as such:

8.8 BMI and Weight Considerations

Norelgestromin and ethinyl estradiol transdermal system is contraindicated in women with a BMI ≥ 30 kg/m² because of the potential increased risk of VTE [see *Contraindications (4) and Warnings and Precautions (5.1)*].

Norelgestromin and ethinyl estradiol transdermal system may be less effective in preventing pregnancy in women who weigh 198 lbs. or more [see *Clinical Studies (14)*].

- vii. **10 OVERDOSAGE** section, 1st sentence: Revise (b) (4) to read, “women.”
- viii. **12.3 Pharmacokinetics** section, *Metabolism* heading, 1st sentence: Revise the beginning of the sentence to read, “Since norelgestromin and ethinyl estradiol are delivered transdermally, first-pass metabolism...”
- ix. **14 CLINICAL STUDIES** section, 2nd paragraph, 1st sentence: Delete (b) (4) after “≥ 198 lbs.”
- x. (b) (4)

2. PATIENT INFORMATION

- a. **What is the most important information I should know about norelgestromin and ethinyl estradiol transdermal system?** section: Revise the entire text as such:

Do not use norelgestromin and ethinyl estradiol transdermal system if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control methods, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Do not use norelgestromin and ethinyl estradiol transdermal system if you have an increased risk for blood clots.

Do not use norelgestromin and ethinyl estradiol transdermal system if your Body Mass Index (BMI) is 30 kg/m² or more. Women with a BMI of 30+ kg/m² or more who use norelgestromin and ethinyl estradiol transdermal system may be at a higher risk for developing blood clots compared to women with a BMI lower than 30 kg/m².

- b. **What is norelgestromin and ethinyl estradiol transdermal system?** section, 1st sentence: Revise the first sentence as such:
Norelgestromin and ethinyl estradiol transdermal system is a birth control patch for women with a BMI less than 30 kg/m².
- c. Delete the sentence, (b) (4) (b) (4) (b) (4) after the chart.
- d. **Do not use norelgestromin and ethinyl estradiol transdermal system if you:** section: Add as the 10th bullet the following:
 - have a BMI of 30 or more
- e. Delete the sentence, “ (b) (4) (b) (4) .
- f. **Norelgestromin and ethinyl estradiol transdermal system may cause serious side effects, including:** section, 1st bullet: Revise the entire bullet as such:
 - **blood clots.** Like pregnancy, hormonal birth control methods increase the risk of serious blood clots (see following graph), especially in women who have other risk factors such as smoking, high blood pressure, high levels of fat in the blood, diabetes, obesity, a family history of blood clots, or age greater than 35. This increased risk is highest when you first start using hormonal birth control and when you restart the same or different hormonal birth control after not using it for a month or more. Some studies have reported that women who use norelgestromin and ethinyl estradiol transdermal system have a higher risk of getting a blood clot. Talk with your healthcare provider about your risk of getting a blood clot before using norelgestromin and ethinyl estradiol transdermal system or deciding which type of

birth control is right for you.

- g. **General information about the safe and effective use of norelgestromin and ethinyl estradiol transdermal system** section, 2nd paragraph: Delete the 1st and 2nd sentences

(b) (4)

(b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

N/A.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

N/A

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

- No deficiencies were identified in Labeling Review #1 (C1) for the labels and labeling submitted on 12/18/19.
- The 3/25/20 submission provides for a representative diagram (i.e., label) of the patch as requested by the drug product quality assessor.

Per 3/25/20 cover letter:

B. Drug Product

FDA Comment # 2

We acknowledge that you provided photographs of transdermal systems used in your bioequivalence study (submission dated December 18, 2019, Module 5.3.1.2, "Image" folder) as well as a representative photograph in your pharmaceutical development report (Module 3.2.P.2, Pharmaceutical Development Report, page 59 of 225, Table 21). However, we were unable to locate a representative diagram of the proposed identifying label. Please submit an image (true to color and size) of the proposed identifying label for the final commercial product. We recommend that this information be included in Module 1.14.1.1.

Amneal's Response:

Amneal acknowledges the Agency's comment and as per the Agency's recommendation, Amneal is hereby providing a representative Patch Diagram of the proposed identifying label for the final commercial product for Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day. Please refer to [Module 1.14.1.1 – Draft Carton and Container Labels – Addendum](#) and [Module 1.14.1.2 Annotated Draft Labeling Text-Addendum for details.](#)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Comparison of CONTAINER Label	
Previous Labeling Review	Currently Proposed
(b) (4)	Ethinyl Estradiol 150/35 mcg per day 150/35 Norelgestromin and Ethinyl Estradiol 150/35 mcg per day 150/35 mcg per day Norelgestromin and Ethinyl Estradiol 150/35 mcg per day 150/35 Norelgestromin and Ethinyl Estradiol 150/35 mcg per day 150/35 mcg per day Norelgestromin and Ethinyl Estradiol 150/35 mcg per day 150/35

Reviewer Comments:

The applicant submitted a representative diagram in Labeling module 1.14. It appears identical to the photo previously submitted in the Quality module. The proposed label is acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

The DRAFT chemistry review, uploaded 5/15/20, had the following assessment for labeling:

Labeling	
Description	
Is the information accurate?	☒ YES ☐ NO
Is the drug product subject of a USP monograph?	☐ YES ☒ NO
Does the labeling need a special USP statement in the Description?	☐ YES ☒ NO
Comment: N/A	
How Supplied	
Is the information accurate?	☒ YES ☐ NO
Are the storage conditions acceptable?	☒ YES ☐ NO
Dosage and Administration	
Is the schematic in product insert (Section 1.14 Labeling) an accurate representation of the actual product design? CHOOSING A PLACE ON THE BODY TO PUT THE PATCH	
	
HOW TO APPLY THE PATCH	
	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any "wrinkles" around the outer edges of the patch.
For OTC Drugs and Controlled Substances	
Is tamper evident feature provided in the container/closure?	Not Applicable
Identifying label present and adequate?	☒ YES ☐ NO
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	☐ YES ☒ NO
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

The comparative analysis review was completed on 3/18/20 with no additional comments.

Portion from 3/18/20 review:

4 CONCLUSION

DCR concludes that minor design differences between the proposed generic Ethinyl Estradiol & Norelgestromin Extended Release Films, 0.035 mg/24HR; 0.15 mg/24HR, submitted under ANDA 213950 and the RS, Xulane[®] (Ethinyl Estradiol & Norelgestromin) films are acceptable.

5 RECOMMENDATION

The Clinical Discipline has completed its comparative analysis review and has no comments.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? NO

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? NO

If Yes, please explain.

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED **NDA** MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

****NDA 021180 is Withdrawn FR as of 07/12/2018:**

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices		32305
NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.	
NDA 021633	Femtra (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg	

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED ANDA MODEL LABELING

ANDA#/Supplement# (S-000 if original): 200910/S-008 (RS)

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR, 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISCN	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR, 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

Supplement Approval Date: 04/24/2020

Proprietary Name: Xulane

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental abbreviated new drug application provides for revisions to the labeling for Xulane and the agreed upon changes to the language included in the Agency's electronic communication dated March 30, 2020. It also refers to the Agency's letter dated January 23, 2020, notifying the applicant, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for transdermal (TDS) contraceptive products. This information pertains to the risk of venous thromboembolic events (VTE) in obese women.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#), or [201.66 \(OTC\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

The previously submitted PI, Patient Information, Instructions for Use labeling were satisfactory in C1 based on the 12/18/19 submission. The applicant did NOT submit these labeling pieces in their 3/25/20 amendment/response to Quality IR. However, the approval of RS ANDA 200910/S-008, approved 4/24/20, supersedes the previous 12/18/19 submission. Thus, the applicant must submit revised PI and Patient Information labeling based on the RS ANDA 200910/S-008 labeling. As the ANDA labeling is not available on Drugs@FDA website, **refer to section 1.1 for detailed comment to the applicant.**

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021180 Annual Report-16, dated 1/16/18]

1 Week Therapy NDC 50458-192-15

Ortho Evra[®]
(norelgestromin/ethinyl estradiol transdermal system)
150/35 mcg/day

Each 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Rx only. For Transdermal Use Only.

Keep out of reach of children, **Package not child resistant.**

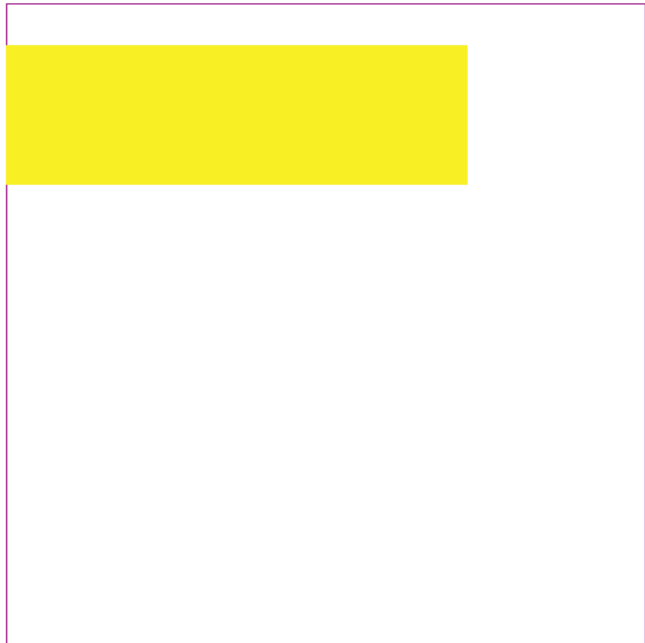
Do not store unpouched. Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Mfg by: Janssen Ortho, LLC Mfg for: Janssen Pharmaceuticals, Inc.
Manati, Puerto Rico 00674 Titusville, New Jersey 08560
© Janssen 2001 10211103



(01)10350458192152



Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your **calendar**.

1	2	3	Week off
First Patch	Second Patch	Third Patch	

Place these stickers on your **pouches**.

ORTHOMcNEIL

©OMP 2001 609-10-680-2 Printed in U.S.A. ORTHO-McNEIL PHARMACEUTICAL, INC. Titusville, New Jersey 08560-0802

NDC 50458-192-15



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems
One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only.
For Transdermal Use Only.

 Janssen

Manufactured by:
Janssen Ortho, LLC
Merrill, Puerto Rico 00674

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day



50458-192-15 5



© Janssen Pharmaceuticals, Inc. 2001
10211803



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

DO NOT REMOVE

 Janssen

excursions permitted to 15 to 30°C (59 to 86°F).
Do not store unopened. Store at 25°C (77°F).
Keep out of reach of children.

IMPORTANT: Each carton contains Detailed Patient Labeling. This should be included with each carton dispensed to the patient.
See package insert.

Each transdermal system is intended to be worn 7 days as prescribed.
150/35 mcg/day
(norelgestromin/ethinyl estradiol
transdermal system)



NDC 50458-192-15

NDC 50458-192-15



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems
One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.
This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
Rx only.
For Transdermal Use Only.

 Janssen

Package not child-resistant.



3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 6/16/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

N/A

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/16/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 021180 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

N/A

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

N/A

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
 Are there changes to the manufacturer/distributor/packer statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment
N/A	N/A	N/A

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	Currently Proposed	Assessment
N/A	N/A	N/A

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	Currently Proposed	Assessment
N/A	N/A	N/A

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	N/A	03/25/2020	Satisfactory
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory in Labeling Review #1
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	
Reminder Sticker	Final	N/A	12/18/2019	
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Revised: 06/2019	12/18/2019	Update and submit
Patient Information		Rev. 06-2019-00	12/18/2019	
Instructions for Use			Rev. 06-2019-00	12/18/2019
SPL Data Elements	N/A	Revised: 6/2019	12/18/2019	



Alison
Park

Digitally signed by Alison Park
Date: 6/17/2020 01:46:32PM
GUID: 506354110000db251c2d2cd0f7476af



Huijeong
Jung

Digitally signed by Huijeong Jung
Date: 6/17/2020 05:58:57PM
GUID: 508da702000287c1e12e719fda6a6d14

LABELING REVIEW

Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs (OGD)
 Center for Drug Evaluation and Research (CDER)

Date of This Review	2/14/2020
ANDA Number(s)	213950
Review Number	1
Applicant Name	Amneal Pharmaceuticals LLC
Established Name & Strength(s) [Add “(OTC)” after strength if applicable]	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Proposed Proprietary Name	None
Submission Received Date	12/18/2019
Primary Labeling Reviewer	Alison Park, Pharm.D.
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

- ACCEPTABLE – No Comments
- Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
- Major Deficiency[†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant

[†]Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

- On Policy Alert List Yes No
- Acceptable for Filing Yes No
- Combined Insert/Outsert Yes No (If yes, indicate ANDA number)

TABLE OF CONTENTS

<u>1</u>	<u>LABELING COMMENTS</u>
	<u>1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT</u> <u>1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE</u>
<u>2</u>	<u>LABELING REVIEW INFORMATION</u>
	<u>2.1 REGULATORY INFORMATION</u> <u>2.2 MODEL PRESCRIBING INFORMATION</u> <u>2.3 PATENTS AND EXCLUSIVITIES</u> <u>2.4 UNITED STATES PHARMACOPEIA (USP)</u> <u>2.5 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)</u>
	<u>2.5.1 DRUG PRODUCT REVIEW</u> <u>2.5.2 DESCRIPTION</u> <u>2.5.3 HOW SUPPLIED/STORAGE AND HANDLING</u> <u>2.5.4 MANUFACTURER, DISTRIBUTOR, AND/or PACKER</u>
	<u>2.6 MODEL CONTAINER LABELS</u>
<u>3</u>	<u>ASSESSMENT OF ANDA LABELING AND LABELS</u>
	<u>3.1 ☐ CONTAINER LABEL (FOR BLISTERS GO TO 3.1.1)</u>
	<u>3.1.1 ☐ UNIT-DOSE BLISTERS</u> <u>3.1.1 ☐ OPHTHALMIC PRODUCTS</u> <u>3.1.2 ☐ INJECTABLE PRODUCTS</u>
	<u>3.2 ☐ CARTON (OUTER OR SECONDARY PACKAGIN) LABELING</u> <u>3.3 ☐ PRESCRIBING INFORMATION</u>
	<u>3.3.1 ☐ MEDICATION GUIDE</u> <u>3.3.2 ☐ OTHER PATIENT LABELING</u> <u>3.3.3 ☐ STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS</u>
<u>4</u>	<u>COMMENTS/CONSULTS FOR OTHER DISCIPLINES</u>
<u>5</u>	<u>OVERALL ASSESSMENT OF MATERIALS REVIEWED</u>

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received December 18, 2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

2 INSTRUCTIONS FOR ASSESSMENT

☒	☐	Check the left checkbox if there is an issue/concern. If a “standard” comment appears, ensure it is appropriate for your situation or enter “freeform” comments if necessary.
☐	☒	Check the right checkbox if there is no issue/concern, or if the question is not applicable. No “standard” comments will appear but reviewers can still enter “freeform” comments if desired.

Freeform Comments:

Enter free text in this section as necessary.

Standard Comments:

- Standardized comments appear in this section for certain questions when left checkboxes are checked.
- Reviewers can modify standardized comments for their situation but should avoid using this section to enter free text comments (i.e. avoid adding additional lines).
- Bullets are preferable to numbers for formatting.

3 LABELING REVIEW INFORMATION

3.1 REGULATORY INFORMATION

☐	☒	Are there any applicable issues in <u>DLR's SharePoint Drug Facts?</u>
☐	☒	Is the drug product listed in the Policy Alert Tracker on <u>OGD's SharePoint?</u>

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED **NDA** MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021180/S-048

****NDA 021180 is Withdrawn FR as of 07/12/2018:**

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804ae997&_afRedirect=1195345493827222

Federal Register / Vol. 83, No. 134 / Thursday, July 12, 2018 / Notices 32305

NDA 021180	Ortho Evra (ethinyl estradiol; norelgestromin) Transdermal Patch, 0.035 mg/24 h; 0.15 mg/24 h.
NDA 021633	Femtra (estradiol acetate) Tablets, 0.45 mg, 0.9 mg, and 1.8 mg

Supplement Approval Date: 08/09/2017

Proprietary Name: Ortho Evra® Transdermal System

Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System

Description of Supplement: This supplemental new drug application provides for revisions to the labeling consistent with the Agency's April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir.

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

MOST RECENTLY APPROVED ANDA MODEL LABELING
 ANDA#/Supplement# (S-000 if original): 200910/S-005
 Supplement Approval Date: 08/09/2017
 Proprietary Name: Xulane
 Established Name: Norelgestromin and Ethinyl Estradiol Transdermal System
 Description of Supplement: This supplemental abbreviated new drug application provides for revisions to the labeling for Xulane consistent with the Agency’s April 26, 2017, letter, notifying the Sponsor, under Section 505(o)(4) of the FDCA, of new safety information that the Agency believes should be included in the labeling for the class of ethinyl estradiol-containing combination hormonal contraceptive products. This information pertains to the risk of elevations of the liver enzyme alanine aminotransferase (ALT) in patients using ethinyl estradiol-containing products concomitantly with direct-acting antiviral combination products that contain ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):
 The RS ANDA 200910 has the following pending labeling supplement:
 • **S-008, pending date 2/12/20:** Mylan Technologies Inc. wishes to supplement the above-referenced Abbreviated New Drug Application (ANDA) with labeling that has been revised in response to the Agency’s January 23, 2020 Safety Labeling Change Notification requesting that Mylan revise our labeling to include “new safety information” concerning a potential reduced efficacy and possible heightened venous thromboembolic events (VTE) risk in obese women. Please note that while Mylan has accepted some of the Agency’s proposed revisions, we are also providing a rebuttal below to reflect our rationale for not accepting other revisions and for including additional text not originally proposed by the Agency.

Reviewer Assessment:

ANDA is **up-to-date** with the RLD/Model labeling

Freeform Comments:

Click here to enter text.

Standard Comments:

3.3 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 2/14/2020

Table 2 provides Orange Book patents for the Model Labeling (NDA 021180) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 2: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
N/A						

Table 3 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 3: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A					

Reviewer Assessment:

☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.

Freeform Comments:

[Click here to enter text.](#)

Standard Comments:

3.4 UNITED STATES PHARMACOPEIA (USP)

The [USP](#) was searched on 2/14/2020

Table 4: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		N/A	N/A
Not Yet Official	NO	N/A	N/A	N/A

Reviewer Assessment:

☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay

Freeform Comments:

[Click here to enter text.](#)

Standard Comments:

3.5 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

3.5.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:

[Click here to enter text.](#)

3.5.2 DESCRIPTION

Table 5: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling	ORTHO EVRA is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, NGMN and EE. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.
ANDA Labeling	(b) (4)

3.5.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 6: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied ORTHO EVRA (norelgestromin/ethinyl estradiol transdermal system) is available in one strength of 150 mcg/day NGMN and 35 mcg/day EE. ORTHO EVRA is a 20 cm² beige, transdermal system heat stamped with ORTHO EVRA. Each system contains 6 mg NGMN and 0.75 mg EE. Each transdermal system is packaged in a protective pouch. ORTHO EVRA is available in folding cartons of 1 cycle each (NDC 50458-192-15); each cycle contains 3 systems. ORTHO EVRA is available for clinic usage in folding cartons of 1 cycle each (NDC 50458-192-24); each cycle contains 3 systems. ORTHO EVRA is also available in folding cartons containing a single system (NDC 50458-192-01), intended for use as a replacement in the event that a patch is inadvertently lost or destroyed. 16.2 Special Precautions for Storage and Disposal Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F). Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

Table 6: Comparison of Model Labeling to ANDA Labeling

ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Norelgestromin and ethinyl estradiol transdermal system is available in one strength of 150 mcg/day NGMN, USP and 35 mcg/day EE, USP. Norelgestromin and ethinyl estradiol transdermal system is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each patch contains 3.15 mg of norelgestromin, USP and 0.289 mg of ethinyl estradiol, USP. Each transdermal system is packaged in a protective pouch. Norelgestromin and ethinyl estradiol transdermal system is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems. 16.2 Special Precautions for Storage and Disposal Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store patches in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer. Used patches still contain some active hormones. The sticky sides of the patch should be folded together and the folded patch placed in a sturdy container, preferably with a child-resistant cap, and the container thrown in the trash. Used patches should not be flushed down the toilet.

3.5.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 7: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4)	<u>Pouch:</u> Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807 <u>Carton:</u> Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807	Distributed by: Amneal Pharmaceuticals LLC Bridgewater, NJ 08807

3.6 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 021180 Annual Report-16, dated 1/16/18)

NDC 50458-192-15

Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems

One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene/polybutene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Rx only.
For Transdermal Use Only.

janssen

Manufactured by:
Janssen Ortho, LLC
Mansfield, Puerto Rico 00674

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day



50458-192-15 5



Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

© Janssen Pharmaceuticals, Inc. 2003
10211803

Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

IMPORTANT: Each carton contains Detailed Patient Labeling. This should be included with each carton dispensed to the patient. See package insert.

Each transdermal system is intended to be worn 7 days as prescribed.

Do not store unopened. Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

Keep out of reach of children.

janssen

NDC 50458-192-15

NDC 50458-192-15

Ortho Evra®
(norelgestromin/ethinyl estradiol
transdermal system)
150/35 mcg/day

Contents: 6 cartons each containing 3 transdermal systems

One 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene/polybutene adhesive, croscopolidone, nonwoven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Rx only.
For Transdermal Use Only.

Package not child-resistant.

janssen

1 Week Therapy NDC 50458-192-15

Ortho Evra[®]

(norelgestromin/ethinyl estradiol transdermal system)
150/35 mcg/day

Each 20cm² system contains 6 mg norelgestromin and 0.75 mg ethinyl estradiol. The inactive components are polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric, lauryl lactate, polyester backing film laminate and polyester release liner.

This product is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Rx only. For Transdermal Use Only.

Keep out of reach of children, **Package not child resistant.**

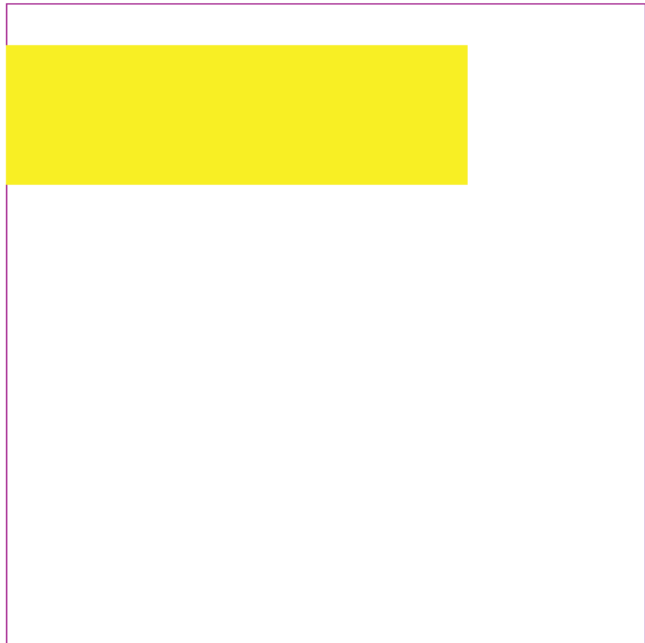
Do not store unpouched. Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F).

See patient instructions. Apply immediately upon removal from pouch. Each transdermal system is intended to be worn 7 days as prescribed.

Mfg by: Janssen Ortho, LLC Mfg for: Janssen Pharmaceuticals, Inc.
Manati, Puerto Rico 00674 Titusville, New Jersey 08560
© Janssen 2001 10211103



(01)10350458192152



Patch Change Reminder Stickers

Place the top row of these stickers on your calendar and the bottom row on your patch pouches to help you remember when to change each patch.

Place these stickers on your **calendar**.

			
First Patch	Second Patch	Third Patch Order refill	

Place these stickers on your **pouches**.

ORTHOMcNEIL

©OMP 2001 609-10-660-2 Printed in U.S.A. ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08860-0602



4 ASSESSMENT OF ANDA LABELING AND LABELS

4.1 CONTAINER LABEL (FOR BLISTERS GO TO 3.1.1)

Reviewer Assessment:

☐	☒	Container meets the too small exemption [21 CFR 201.10(i)].
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Title case is used in expressing the established/proprietary name
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement.
☐	☒	Usual dosage statement
☐	☒	NDC number as linear bar code
☐	☒	Orientation of linear bar code [21 CFR 201.25(c)(2)]
☐	☒	Expiration date and lot number (or placeholder)
☐	☒	Equivalency statement (product strength)

☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)]
☐	☒	Controlled substance symbol
☐	☒	Image of drug product represents the true size, color, and imprint
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)]
☐	☒	Latex warning statement is properly displayed [21 CFR 201.10(d)(2)].
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means
☐	☒	Labels of proposed product is differentiated from related products
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable and has address listed correctly
☐	☒	Tamper evident (controlled substances) requirements are met

Freeform Comments:

[Click here to enter text.](#)

Standard Comments:

4.1.1 UNIT-DOSE BLISTERS

4.1.1 OPHTHALMIC PRODUCTS

4.1.2 INJECTABLE PRODUCTS

4.1.2.1 CONTAINER LABEL FOR PARENTERAL SOLUTIONS

4.1.2.2 CONTAINER LABEL FOR SOLID INJECTABLE

4.1.2.3 CONTAINER LABEL FOR PHARMACY BULK PACKAGE

4.2 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

☐	☒	The answers to the Container Label questions are the same for the Carton Labeling.

Freeform Comments:

4.3 PRESCRIBING INFORMATION

Reviewer Assessment:

☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) .
☐	☒	Patent/exclusivity carve out is acceptable.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable and has address listed correctly
☐	☒	STIC requirements addressed appropriately
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly
☐	☒	Revision date appears at end of HIGHLIGHTS section
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201): Sulfite (21 CFR 201.22) Yellow #5 (Tartrazine) (21 CFR 201.20) Phenylalanine/aspartame (21 CFR 201.21) Latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)]
☐	☒	Gluten statement is appropriately stated.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(D)]
HOW SUPPLIED/STORAGE and HANDLING:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed
☐	☒	NDC numbers are present
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin)
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph.
☐	☒	"Discard unused portion" for single-dose products

Freeform Comments:

Click here to enter text.

Standard Comments:

4.3.1 MEDICATION GUIDE

4.3.2 OTHER PATIENT LABELING

Reviewer Assessment:

☐	☒	Other patient labeling is the same as the model labeling except for allowable differences.

Freeform Comments:

- The proposed patient information labeling and information for use (IFU) are identical with the RLD except for allowable differences, including the Quality information.
- Note that the comparative analysis assessment is still pending with the Division of Clinical Review (DCR).

4.3.3 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Table 8: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Drug Product Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

☐	☒	Applicant submitted SPL
☐	☒	Data elements (strength, inactive ingredients, product characteristics, packaging etc.) are consistent with the information submitted in the ANDA labeling.

Freeform Comments:

[Click here to enter text.](#)

Standard Comments:

5 COMMENTS/CONSULTS FOR OTHER DISCIPLINES

A labeling statement required verification from another division discipline

Reviewer Assessment:

☐	☐	Rubber
☐	☐	Latex
☐	☐	Gluten
☐	☐	Alcohol (ethanol)
☐	☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	☐	Sulfite
☐	☐	Phenylalanine (aspartame) – content calculation
☐	☐	Yellow #5 (tartrazine)
☐	☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)

☒	☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Freeform Comments:

FYI ISSUE for the Drug Product Quality Assessor: Alert the labeling reviewer if the statement of content of each patch is not accurate in the labeling (e.g., Each 12.5 cm system contains 3.15 mg norelgestromin, USP and 0.289 mg ethinyl estradiol, USP) as this affects the pouch and carton labeling as well as the prescribing information labeling.

6 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 9: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Transdermal System	N/A	(b) (4)	12/18/2019 (QOS submission)	Satisfactory
Pouch	Final	150/35 mcg per day – Contains 1 patch	12/18/2019	Satisfactory
Carton	Final	150/35 mcg per day -Carton containing 3 pouches containing 1 patch each	12/18/2019	Satisfactory
Reminder Sticker	Final	N/A	12/18/2019	Satisfactory

Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Final (submitted) Draft (reviewed)	Revised: 06/2019	12/18/2019	Satisfactory
Patient Information		Rev. 06-2019-00	12/18/2019	Satisfactory
Instructions for Use		Rev. 06-2019-00	12/18/2019	Satisfactory
SPL Data Elements	N/A	Revised: 6/2019	12/18/2019	Satisfactory

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

CHEMISTRY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA 213950 Assessment #1

Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Dosage Form	Transdermal System
Strength	150 mcg Norelgestromin per day / 35 mcg Ethinyl Estradiol per day
Route of Administration	Transdermal
Rx/OTC Dispensed	Rx
Applicant	Amneal Pharmaceuticals LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0001 Pre-submission Facility Correspondence	10/16/2019	Facility
0002 Original Submission	12/18/2019	All
0003 Filing IR Response	01/29/2020	DP
0005 Quality TCIR Response	03/25/2020	DS/DP
0006 Quality TCIR Response	04/15/2020	Biopharm
0007 File for an Extension in DRL Response	06/12/2020	All
0008 Response to DRL	06/22/2020	All
0010 Response to DP IR	07/29/2020	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
DS – Norelgestromin (NGMN)	Yongliang Zhang	Neeru Takiar
DS – Ethinyl Estradiol (EE)	N/A	N/A
Drug Product	Pinaki Desai	Robert Berendt
Manufacturing	James Norman	Yubing Tang
Microbiology	N/A	N/A
Biopharmaceutics	Kalpana Paudel	N/A
Regulatory Business Process Manager	Steven Yang	
Application Technical Lead	Robert Berendt	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	<i>Drug Substance:</i> Norelgestromin	Adequate with Additional Comments	07/08/2020	Yongliang Zhang Additional Comment pertains to elemental impurity risk assessment
	II		<i>Drug Substance:</i> Ethinyl Estradiol	Adequate	05/17/2017	Reviewer David Skanchy marked (SD#208) as NAI No new information submitted after last review
	IV		(b) (4)	Adequate	09/17/2019	Reviewer Cedar Boakye marked it as adequate and no new information is submitted thereafter
	III			N/A	N/A	N/A
	III			N/A	N/A	N/A
	III			N/A	N/A	N/A

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
RLD	NDA 021180	Ortho Evra (Withdrawn 2015); Janssen Pharmaceuticals Inc.
RS	ANDA 200910	Xulane; Mylan Technologies Inc.

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product during the expiration dating period of 24 months.

- The applicant has provided acceptable raw material, in-process, and finished product controls.*
- The applicant has established an adequate in vitro drug release specification (method and acceptance criteria) for routine quality control of the finished product.*
- The overall facility assessment recommends approval.*
- The labels have adequate quality information.*

Therefore, from the quality perspective, this ANDA is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The basis for the Applicant's ANDA is the approved reference standard (RS), Xulane® (ANDA 200910, Mylan), listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book). The reference listed drug product (Ortho Evra®, NDA 21180, Janssen) was withdrawn from the market in 2015, not due to reasons of safety or efficacy.

The drug product is a transdermal system (TDS) in one strength intended to deliver a nominal amount of 150 mcg per day norelgestromin and 35 mcg per day ethinyl estradiol over the 7-day wear period. The TDS is a 12.5 cm² system with rounded corners with tan backing printed with "Norelgestromin and Ethinyl Estradiol 150/35 mcg per day" in brown ink, protected with a removable translucent oversized dimple slit-release liner. Each TDS is packaged in a protective pouch and is available in folding cartons of 1 cycle each (NDC 69238-1521-3); each cycle contains 3 systems.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Store TDS in their protective pouches. Apply immediately upon removal from the protective pouch. Do not store in the refrigerator or freezer.

Used TDS still contain some active hormones. The sticky sides of the TDS should be folded together and the folded TDS placed in a sturdy container,

preferably with a child-resistant cap, and the container thrown in the trash. Used TDS should not be flushed down the toilet.

Final recommended dissolution method/specification acknowledged by Firm?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many: _____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	☒ Yes *(see comments) ☐ No ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	☒ Yes ☐ No *(see comments) ☐ N/A
Comments: USP monographs exist for both drug substances, and the Applicant's specifications comply. No USP monograph exists for the drug product.	

Proposed Indication(s) including Intended Patient Population	Norelgestromin and ethinyl estradiol transdermal system is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women with a BMI < 30 kg/m ² for whom a transdermal delivery system is an appropriate method of contraception.
Duration of Treatment	Chronic 28-day cycle: Apply a new TDS to the upper outer arm, abdomen, buttock, or back each week for three weeks (21 total days); week four is TDS-free.
Maximum Daily Dose	MDD is one TDS per day Each TDS contains 3.15 mg norelgestromin and 0.289 mg ethinyl estradiol
Alternative Methods of Administration	• TDS may be applied on the upper outer arm, abdomen, buttock, or back • Wear only one TDS at a time • Do not cut or alter the TDS in any way

B. Quality Assessment Overview (Please note: ATLS should check the most recent policy alert list)

Drug Substance, Drug Product, and Labeling

Norelgestromin (NGMN) USP

DMF (b) (4) for norelgestromin USP, (b) (4), has been assessed by DLAPI and found adequate. The ANDA Applicant's DS

specification complies with the current USP monograph. Norelgestromin exists as a mixture of two geometrical isomers (anti and syn) which have the same activity (b) (4). It does not have any known polymorphism and is non hygroscopic.

Ethinyl Estradiol (EE) USP

DMF (b) (4) for ethinyl estradiol USP, (b) (4), has been assessed by DLAPI and found adequate. The ANDA Applicant's DS specification complies with the current USP monograph. (b) (4)

(b) (4)

(b) (4) The DS is hygroscopic, and a limit for water content is included in the specification.

NGMN and EE Transdermal System

The drug product is a matrix-type transdermal system consisting of three layers: 1) The backing layer is a tan pigmented polyethylene and polyester film; 2) the middle layer is the drug-in-adhesive matrix, (b) (4) polyisobutylene/polybutene adhesive (b) (4) polybutene (b) (4) (b) (4), crospovidone (b) (4), oleyl alcohol (b) (4) and dipropylene glycol (b) (4) (b) (4); and 3) the third layer is (b) (4) polyethylene terephthalate (PET) release liner film with silicone coating that is removed just prior to application. (b) (4),

(b) (4)



Biopharmaceutics

The Applicant has followed the FDA database in vitro release method for Norelgestromin and Ethinyl Estradiol Transdermal System, 150 mcg/35 mcg per day. The Applicant conducted studies for formulation variants and process parameters identified as potentially high-risk variables during risk assessments to

(b) (4)

(b) (4)

The following in vitro drug release method and acceptance criteria are adequate for quality control of the finished product:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
FDA database method	V – Paddle Over Disk	50	0.1% Hydroxypropyl-Beta-cyclodextrin / 32 ± 0.5°C	900 mL	Norelgestromin 0.5 hr: (b) (4) 2 hr: % 12 hr: NLT (b) (4)
					Ethinyl Estradiol 0.5 hr: (b) (4) 2 hr: % 12 hr: NLT (b) (4) %

Shelf Life

The Applicant provided 6 months of ACC and 18 months of long-term (CRT) stability results from three exhibit batches. All stability results comply with the final specification (including final IVRT acceptance criteria) and do not show

significant trending. Thus, per ICH Q1E, the provided results are adequate to support the proposed 24-month shelf life.

Policy Alerts

No relevant policy alerts exist per the OGD Policy Alert List dated 07/20/2020.

Lifecycle Considerations

- *Facility:* Note for future inspections: Page 23 of 3.2.P.3.4 indicates that labeling accountability in the range of (b) (4) % is acceptable. This may not be compliant with 21 CFR 211.125 Labeling Issuance.

C. Risk Assessment

Drug Product CQAs		Initial Risk Ranking	Comments	Updated Risk After Cycle #1	Comments*
Physical Stability	Drug Substance	48 Moderate			
	Matrix Formulation	32 Moderate			
Chemical Stability		12 Low			
Assay	Drug Substance	18 Low			
	Critical Excipient	27 Moderate			
Content Uniformity	Drug Substance	32 Moderate			

(b) (4)

Drug Product CQAs		Initial Risk Ranking	Comments	Updated Risk After Cycle #1	Comments*
			(b) (4)		
	Critical Excipient	24 Low			
Adhesive Properties		40 Moderate			
Cohesive Properties		64 High			

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk After Cycle #1	Comments*
		(b) (4)		
Delamination	16 Low			
Drug Release/In Vitro Release	100 High			
Dose Dumping (Heat Effect)	64 High			

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk After	Comments*
		(b) (4)		
Microbial Limits	9 Low			

Application Technical Lead Name and Date: Robert Berendt, 07/31/2020



Robert
Berendt

Digitally signed by Robert Berendt

Date: 7/31/2020 06:20:27PM

GUID: 508da7380002b309c612f7e27bdf5995

RECOMMENDATION

☒ Adequate
☐ Complete Response-Minor
☐ Complete Response-Major
☐ Complete Response-Major-Facilities Only

OLDP Drug Product Review

Overview	
ANDA No.	213950
Assessment Cycle No.	1
RLD/RS No.	RLD: N21180: Ortho Evra
	RS: A200910: Xulane
ANDA Applicant	Anneal Pharmaceuticals LLC
Drug Product (DP) manufacturer (if different from applicant)	-
Dosage Form	Transdermal System (TDS)
Route	Transdermal
DP Name	Norelgestromin and Ethinyl Estradiol Transdermal System
Strength (s)	150/35 mcg per day
DRUG SUBSTANCE #1	
Drug Substance (DS) Name	Norelgestromin
Type II DMF Number	(b) (4)
Type II DMF Holder	(b) (4)
Type II DMF Status	Pending Review
DRUG SUBSTANCE #2	
Drug Substance (DS) Name	Ethinyl Estradiol
Type II DMF Number	(b) (4)
Type II DMF Holder	(b) (4)
Type II DMF Status	No Action Indicated (NAI)

Drug Substance #1: Norelgestromin, USP

Review Recommendation: Adequate

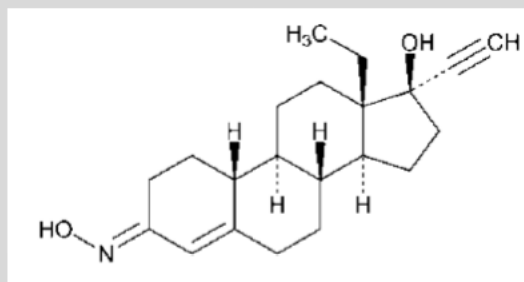
Theme:

☐ N/A	☐ Other (Requires Division Director Approval)
☒ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

N/A

DS structure:



Chemical Name: – (17α)-13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one-oxime
 – 18,19-dinorpregn-4-en-20-yn-3-one,13-ethyl-,17-hydroxy, 3-oxime, (17-α)-
 – 13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime

Chemical Formula: C₂₁H₂₉NO₂ **MW:** 327.47 g/mol

CAS #: [53016-31-2]

DS USP Status:

- Compendial
- Non-Compendial
- USP monograph about to become official (in Upcoming USP editions)

Review Summary: The drug substance, norelgestromin is a white or almost white powder with very low aqueous solubility. It exists as a mixture of two geometrical isomers (anti and syn) which have the same activity (b) (4). It does not have any known polymorphism. DS is non hygroscopic. DMF was found adequate by reviewer Yongliang Zhang on July 08, 2020.

Highlight Key Outstanding Issues from Previous Sequences: N/A

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): N/A

Additional Evaluation (if needed): Adequate

Links – [Reference standard](#)

S6. Drug Substance Container Closure System

Applicant refers DMF for container closure system

Additional Evaluation (if needed): Adequate

S7. Drug Substance Stability

Applicant refers DMF for stability data

Applicant's DS retest period – (b) (4)

Additional Evaluation (if needed): Adequate

(b) (4)

Deficiencies: See compiled list of DS deficiencies at the end of the document

Drug Product

Review Recommendation: *Inadequate - Minor*

☐ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

DP USP Status:

Compendial

Non-Compendial

USP monograph about to become official (in Upcoming USP editions)

Review Summary:

The drug product is a transdermal drug delivery system for contraception consisting of two drug substances (norelgestromin and ethinyl estradiol). Per the orange book, Ortho Evra® has been withdrawn (on Oct. 30, 2015) from the market not due to safety of efficacy reasons. Approved product, Xulane (ethinyl estradiol/norelgestromin TDS), under ANDA 200910 has been designated as the reference standard. RLD, RS and ANDA product designs are similar. Generic product is a single-layer matrix TDS with a non-cross-linked polyisobutylene/polybutene-based adhesive. (b) (4)

(b) (4). The transdermal system contains 3.15 mg of norelgestromin and 0.289 mg ethinyl estradiol per 12.5 cm² patch, delivering 150 mcg of norelgestromin and 20 mcg of ethinyl estradiol per day over a 7-day period.

Applicant provided 6 M ACC and 18 M CRT stability data for 3 exhibit batches, and the stability results meet the specification. Per ICH Q1E, the 18 M long-term stability data can be extrapolated to support the Applicant’s proposed shelf life of 24 M,

Applicant provide sufficient information to assure the quality of the drug product.

From CMC perspective, ANDA 213950 is approvable.

Highlight Key Outstanding Issues from Previous Sequences: N/A

Concise Description Outstanding Issues Remaining:

Bioequivalence is assessing whether the drug loading is sufficient to maintain drug delivery over the labeled wear period - BE Review pending.

List Number of Comparability Protocols (ANDA only): N/A

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: Non-compendial*
- *Dissolution status: Applicant accepted the Agency’s recommended specification in the DRL response dated June 22, 2020*
- *Elemental impurity compliance with ICH Q3D – status: Complies*
- *Number of Comparability protocols included: None*

P1. Drug Product Description

RLD Transdermal DP Overview	
Referenced RLD/RS No.	RLD: N21180: Ortho Evra RS: A200910: Xulane The RLD product is discontinued. Please note that Federal Register determined that RLD ORTHO EVRA® was not discontinued or

	withdrawn for safety or efficacy reasons. FDA has initiated a withdrawal of the application as voluntarily requested by the sponsor because sponsor has stopped marketing drug product.
RLD/RS Indication(s)	It is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch
RLD/RS sponsor	RLD: Janssen Pharmaceuticals RS: Mylan Technologies Inc.
Proprietary Name	RLD: ORTHO EVRA RS: XULANE
RLD/RS Strength(s)	Norelgestromin 150/Ethinyl Estradiol 35 mcg per day
RS's notable quality considerations/aftermarket problems Xulane	The highlighted information in this table is excerpted from A200910 based on information in the CDER internal transdermal DDS database: ☐ Cold Flow ☐ Crystals ☒ Adhesion Problems ☐ Adhesive Problems ☐ Post Approval Product Changes ☒ Other <i>Explain other:</i> • Some of the periodic adverse drug experience reports include application site pruritus, rash, pain, erythema. Other complaints indicate adhesion issues such as the patch not sticking well or the patch falling off after short period of wear or during showering and very few report (1 report) of cold flow described as the adhesive coming off the patches. • Identifying label wears off and is completely gone by the end of the 7-day wear period. • The labeled strength of 150 mcg/35 mcg per day is likely inaccurate due to reliance on the RLD's labeled nominal strength (refer to RLD aftermarket problems below).
RLD's notable issues/aftermarket problems Ortho Evra	The highlighted information in this table is excerpted from N21180 based on information in the CDER internal transdermal DDS database: ☐ Cold Flow ☐ Crystals ☒ Adhesion Problems ☒ Adhesive Problems ☐ Post Approval Product Changes ☒ Other <i>Explain other:</i>

	• Determination of delivery rate by sponsor was done by calculation and sponsor had not performed any residual drug analysis, which was a source of concern to the agency. • There have been some reports of adhesion failure (patch falling off or partially detaching) such that the patients required supplementary adhesion with plasters or tapes to keep the patches on. There were also application site-related pruritus and irritation. • Equilibration period needed to ensure proper drug release.
Prescribed period of TDDS wear	7 Days

ANDA DP Sample Assessment

ANDA and RLD DP Samples Requested	☐ YES ☒ NO
*According to current agency practice, high-resolution photographs are requested	

Comments and Images (as needed): Following image is from section P.2.
(b) (4)

In response to TCIR (March 25, 2020), applicant provided legible image of actual DP showing proposed identifying label and labeling was notified about this change:

	Ethinyl Estradiol	
Day	150/35 mcg per day	150/35 mcg per day
Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol
150/35 mcg per day	150/35 mcg per day	150/35 mcg per day
Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol
150/35 mcg per day	150/35 mcg per day	150/35 mcg per day
Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol
150/35 mcg per day	150/35 mcg per day	150/35 mcg per day
Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol	Norelgestromin and Ethinyl Estradiol
150/35 mcg per day	150/35 mcg per day	150/35 mcg per day

Patient-Product Interface (Strength Attributes; information from 1.14, P.1 and P.7)

Strength(s)	Active Layer Area (cm ²)		DP Size (cm ²)		Dry Coat Weight (mg)	Drug Content (mg)	Residual DS (mg)*	CCS Design
	RS	TEST	RS	TEST				
Norelgestromin 150/Ethinyl Estradiol 35 mcg per day	14 cm ²	12.5 cm ²	14 cm ²	12.5 cm ²	131.25	Norelgestromin 3.15 mg/Ethinyl Estradiol 0.289 mg	Norelgestromin 1.07 mg/Ethinyl Estradiol 0.170 mg	(b) (4)

ANDA TDS Design

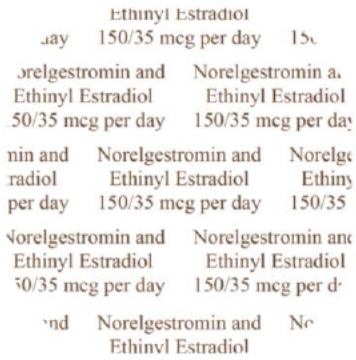
Insert ANDA DP schematic elaborating different components below (i.e., copy/paste schematic from P.1 of submission): Norelgestromin and ethinyl estradiol transdermal system is a thin, matrix-type transdermal system consisting of three layers. The backing layer is composed of a tan backing consisting of pigmented polyethylene and polyester. It provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, polybutene, crospovidone, oleyl alcohol and dipropylene glycol as inactive components. The active components in this layer are the hormones, norelgestromin, USP and ethinyl estradiol, USP. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a silicone coating on the side that is in contact with the middle adhesive layer.

The cross-section Diagram:



Slit, Siliconized Polyester	Release Liner (Oversized and dimpled)

	Generic Design	Comparison to RLD/RS
State of DS in Matrix	Homogenous	Homogenous

ANDA's Identifying Label	Ink Acceptable: ☒YES ☐NO (Label must include DP name & strength at least) Explain other: N/A Insert actual ANDA DP picture here for all strengths:  (b) (4)	Ink Insert actual RLD/RS DP picture here for all strengths:   RLD (Ortho Evra) Identifying label is deboss/emboss
Release Liner (RL)	Select all that applies ☒Slit ☒Oversize ☐Not Oversize ☐Oversize tearable ☐Overlapping ☒Dimples ☐Slip Liner	Select all that applies RLD/RS: ☒Slit ☒Oversize ☐Not Oversize ☐Oversize tearable ☐Overlapping ☐Dimples ☐Slip Liner
Rate Controlling Membrane	☐YES ☒NO	Not present in RLD
Adhesive Overlay	☐YES ☒NO	☐YES ☒NO
Metal Backing	☐YES ☒NO	Not present in RLD
Slip Sheet	☐YES ☒NO	Different from RLD RS (Xulane) contains underlay and overlay slips (release liner) in pouch
Additional Components	☐YES ☒NO	☐YES ☒NO

	Additional Component's Description: N/A	Additional Component's Description: N/A

Do the differences between ANDA and RLD formulation design / excipient composition present potential quality concerns?

YES NO

Concern: Does Amneal's product have sufficient ethinyl estradiol drug load?

The information in this table is excerpted from N21180, A200910 and A213977:

- Amneal BE studies were performed on the abdomen. Xulane (Mylan) BE studies were performed on left or right upper back. For this product labeling notes that absorption is slightly lower from abdomen than other anatomic sites (upper outer arm, buttock, or back).
- The drug load for the proposed drug product is less compared to RS or RLD. The ethinyl estradiol drug load in ANDA 213950 is (b) (4) micrograms.
- If we assume that the EE delivery rate at a non-abdomen site is close to the value indicated in Mylan's Xulane residual drug study, then the EE delivery rate is (b) (4). Even if all drug is depleted over the 7-day wear period (i.e., 0% residual drug), the total drug load would need to be (b) (4) mcg EE per TDS.
- Further, residual drug studies submitted in multiple ANDAs (200910, 213950, and 213977) are inconsistent with respect to the amount of delivered drug – potentially due to differences in application site (abdomen vs. upper back). This issue is discussed under section P.2. – Residual drug.
- OGD (BE and Clinical) was contacted on March 17, 2020, regarding the concern of insufficient drug loading. BE met with ORS for further discussion and submitted a consult to DQMM to perform PK modeling to support whether another biostudy on a non-abdomen application site is needed to support the application. Further, in the Bioequivalence DRL, BE requested the applicant to provide justification for low drug load for EE and application of DP on non-abdominal sites. The DQMM consult response (dated July 15, 2020) concluded that “our analysis indicates that the Test and RS are expected to be BE and no EE depletion is expected for the Test drug product when the product is applied on the back of healthy volunteers under the labeled use conditions (no overlay). DQMM hypothesized that the higher drug delivery noted in prior applications may have arisen due to the use of an adhesive overlay during the clinical PK studies, or due to differences in the subject population involved in the PK studies. The BE review remains pending as of July 30, 2020. The clinical review is adequate, with conclusion that Skin irritation-sensitization study and adhesion are adequate.

Links: [Comparative Analysis](#), [Labeling Review](#)

Reviewer Evaluation

Assessment – Adequate from the Quality perspective

Identifying Label: The applicant submitted image (true to color and size) of the proposed identifying label in response to TCIR (March 25, 2020). Proposed identifying label for DP contains full name of both APIs and strength of TDS and the photographs of TDS systems used in the BE study are provided in 5.3.1.2. These photographs demonstrate poor durability of the identifying label for the Xulane over the 7-day wear period,

however the generic product identifying label showed slight fading but it appears to be legible after 7 day wear period. Hence, identifying label and information submitted is adequate from quality prospective. The comparative analysis for this drug product is adequate and no clinical concerns were identified. Further, labeling discipline found identifying label to be adequate.

Difference between RLD/RS and generic: Although OPQ raised the concern regarding sufficient drug load in the test product, this is fundamentally a Bioequivalence issue (not a Quality issue) and therefore is within the purview of OGD/Division of Bioequivalence and outside the scope of the OPQ Quality assessment. Therefore, no quality deficiency will be issued on this topic.

DP Component Composition of ANDA Drug Product

Ingredients	Quantity in mg/patch	Quantity in %w/w	Function
Ethinyl Estradiol, USP (b) (4)	0.289	(b) (4)	API
Norelgestromin, USP	3.15	(b) (4)	API
Polyisobutylene/Polybutene Adhesive (b) (4)	(b) (4)	(b) (4)	(b) (4)
Polybutene (b) (4)	(b) (4)	(b) (4)	(b) (4)
Crospovidone, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Oleyl Alcohol, NF (b) (4)	(b) (4)	(b) (4)	(b) (4)
Dipropylene Glycol (b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	100	-

(b) (4)

Ingredients	Size / Patch	Function
(b) (4) (Pigmented Polyethylene and Polyester printed with Norelgestromin and Ethinyl Estradiol Transdermal System 150/35mcg per day)	12.5 cm ²	Backing Film
(b) (4) (polyethylene terephthalate film with silicone coating) (6 inch wide)	> 12.5 cm ² , oversized release liner	Release Liner

(b) (4)

Reviewer Evaluation

Assessment – Adequate

Composition: The qualitative and quantitative compositions and function of each component for all strengths of the drug product are appropriately provided. The size of the proposed TDS (12.5 cm²) is smaller compared to RS (14 cm²) and RLD (20 cm²). (b) (4)

(b) (4)

Proposed formulation contains same excipients as RLD/RS. RLD/RS and ANDA product designs are similar, except Xulane contains non-woven fabric as support for adhesive. The inactive ingredients in generic product are either same or very similar to RS functionality wise.

Quantities of the excipients and adhesives are different in ANDA product compared to RS. Refer to Xulane and Ortho Evra compositions below:

The information excerpted from ANDA 200910 and NDA 21180:

Mylan and Ortho Evra Composition

Saved to M: Drive

ANDA 200910			NDA 21180		
Components	% w/w	mg/patch	Components	% w/w	mg/patch
Norelgestromin	(b) (4)	4.86	Norelgestromin	(b) (4)	6.00
Ethinyl Estradiol		0.53	Ethinyl Estradiol		0.75
Dipropylene Glycol		(b) (4)			(b) (4)
Light Mineral Oil, NF					
Crospovidone					
Polyisobutene Adhesive			Polyisobutylene/ Polyisobutene Adhesive		
Oleyl Alcohol, NF			Lauryl Lactate		
Total Adhesive matrix	100.00				

Mylan – 14 cm²

Ortho Evra – 20 cm²

(b) (4)

(b) (4)

Components: Selected backing membrane, release liner and pouching material for Amneal's product are based on Xulane. Xulane contains oversized release liner with slit and TDS is packaged with additional pieces of protective film above and below the system within each pouch.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Elemental Iron: The portion of proposed TDS which has contact with the skin contains no elemental iron; therefore, this product is in compliance with 21 CFR Part 73.1200(c).

Inactive Ingredient Report: Quantities for other ingredients are within the IIG limits. Refer to table below. The ingredients used in the formulation have either been listed in the IIG for other transdermal manufacturers or approved in controlled correspondence with FDA. Amneal submitted ODG control correspondence to assess the proposed levels of adhesive Polyisobutylene/Polybutene Adhesive (b) (4) and Polybutene (b) (4). The outcome of the control was adequate.

MDE:

	The woman should tear open the pouch at the top edge. She should peel open the foil pouch that contains the patch and its clear plastic cover. She should gently remove the patch and its plastic cover together from the pouch, being careful not to separate the patch from the clear plastic cover.	
	Using a fingernail, the woman should peel away half of the clear plastic. She should avoid touching the sticky surface with her fingers.	
	The woman should apply the sticky side of the patch on the skin she has cleaned and dried. She should then remove the other half of the clear plastic and attach the entire patch to her skin.	
	- The woman should press firmly on the patch with the palm of her hand for 10 seconds, making sure that the whole patch adheres to her skin. - She should run her fingers over the entire surface area to smooth out any “wrinkles” around the outer edges of the patch.	

For OTC Drugs and Controlled Substances

Is tamper evident feature provided in the container/closure?	Not Applicable
Identifying label present and adequate?	☒ YES ☐ NO
Any issue(s) sent to and/or received from the OGD Labeling Reviewer	☐ YES ☒ NO
Reviewer Comment	
Identifying label is present and found adequate from quality perspective. DCR will also assess adequacy of identifying label.	

Deficiencies –

DS: None

DP: None

Labeling: None



Robert
Berendt

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Pinaki
Desai

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Date: 8/03/2020 08:08:04AM
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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 213950
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day
Strengths	150/35 mcg per day
Dosage Form	Transdermal System
Administration Route	Transdermal
Indication	estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch.
Applicant Name	Amneal Pharmaceuticals LLC
RLD Number	N021180

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

The proposed product is a single-layer, matrix transdermal system. (b) (4)

(b) (4)

(b) (4).

At the end of review cycle #1, the facilities and manufacturing process are approvable.

It is possible that this application will receive a major CR from other disciplines due to a difference in total drug load between the RLD, reference standard, and proposed generic products. See the “Other Considerations” section of this assessment. If a reformulation is required or if new batches are manufactured, the facilities and process will need to be reevaluated.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
Pre-submission facility correspondence (SD#1)	10/16/2019
Original submission (SD#2)	12/18/2019
Response to filing IRs (SD #3)	01/29/2020
Response to clinical IRs (SD#4)	02/18/2020
Response to OPQ IRs (SD#5)	03/25/2020
Response to OPQ DRL (SD#8)	06/22/2020

Highlight Key Issues from Last Cycle and Their Resolution: n/a

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

List Number of Comparability Protocols: Zero, none submitted

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	Yes (#Lifecycle)
Facility implementation issues (#Implementation)	
Note for future inspections: Pg 23 of 3.2.P.3.4 indicates that labeling accountability in the range of 95-105% is acceptable. This may not be compliant with 21 CFR 211.125 <i>Labeling Issuance</i> .	

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			

No evaluation is necessary for the following facilities listed in P.3.1:

-
-
-
-
-
-

(b) (4)

II. Drug Product Manufacturing

1. Batch Formula

Assessment: Adequate

Product design:

This is a single-layer matrix TDS with a non-cross-linked polyisobutylene/polybutene-based adhesive. The APIs are dissolved and povidone is dispersed in the matrix. The adhesive contains two permeation enhancers: dipropylene glycol and oleyl alcohol.

(b) (4)

2. Commercial Process Flow Diagram

Assessment: Adequate

(b) (4)

4. Pre-Approval Inspection Summary : N/A

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table	
N/A	

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	James Norman		3/18/2020 3/31/2020 06/25/2020 06/29/2020	Adequate	Approve
Choose an item.		Yubing Tang 4/1/2020 6/28/2020 6/29/2020	3/29/2020	Choose an item.	Choose an item.
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.



James
Norman

Digitally signed by James Norman

Date: 6/29/2020 12:55:46PM

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Yubing
Tang

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Date: 6/29/2020 01:13:00PM

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BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	213950-ORIG-1
Product Name	Norelgestromin (NG) and Ethinyl Estradiol (EE) Transdermal System, 150 mcg/35 mcg per day
Applicant	Amneal Pharmaceuticals LLC
Dosage Form/Strengths	Transdermal Delivery System (TDS)/ 150 mcg/35 mcg per day
Route of Administration	Transdermal
Indication for Use	Estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch.
RLD/RS	RLD: Ortho Evra® (norelgestromin and ethinyl estradiol) TDS, 150 µg /35 µg/day RS: Xulane® (norelgestromin and ethinyl estradiol), 150 µg /35 mcg/day TDS
Submission Date	Original:10/16/2019 IR response: 04/15/2020 IR response: 06/22/2020
Review Date	03/05/2020; 05/26/2020; 07/14/2020
Primary Reviewer	Kalpana Paudel, Ph.D.
Secondary Reviewer	NA
Recommendation	ADEQUATE

1. REVIEW SUMMARY:

Background:

The proposed drug product, Norelgestromin (NG) and Ethinyl Estradiol (EE) Transdermal System, 150 mcg/35 mcg per day, is a generic product of the reference listed drug (RLD) Ortho Evra®, 150 mcg/35 mcg per day by Janssen Pharmaceuticals, Inc. under NDA# 021180. However, since Ortho Evra® has been withdrawn from sale for reasons other than safety and efficacy, the Applicant used the reference standard selected by the FDA, Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System), 150 mcg/35 mcg per day by Mylan Technologies, Inc. under ANDA 200910 for in vivo bioequivalence studies.

Submission:

The Applicant has submitted the in vitro drug release method, the drug release data for the proposed drug product and the RLD and proposed drug release acceptance criteria as the quality control (QC) tool.

Review's Objective:

The review is focused on evaluation of the proposed in vitro drug release method and acceptance criteria.

Reviewer's Assessment:

The following in vitro drug release method and acceptance criteria are approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
FDA database method	V – Paddle Over Disk	50	0.1% Hydroxypropyl-Beta-cyclodextrin / 32 ± 0.5°C	900 mL	Norelgestromin 0.5 hr: (b) (4) 2 hr: (b) (4) % 12 hr: NL (b) (4) Ethinyl Estradiol 0.5 hr (b) (4) % 2 hr: (b) (4) 12 hr: NL (b) (4)

Conclusion and Recommendation:

From Biopharmaceutics perspective, ANDA 213950 is adequate for approval.

2. SUBMISSION CONTENT CHECKLIST:

INFORMATION		YES	NO	N/A
1	Is there a USP release method?	☐	☒	☐
2	Did the Applicant use the USP release method?	☐	☐	☒
3	Is there an FDA-Database release method?	☒	☐	☐
4	Did the Applicant use the FDA-Database release method?	☒	☐	☐
5	Did the Applicant conduct release testing with a proposed in-house release method?	☐	☒	☐
6	Did the Applicant use 12 individual units of the test (proposed) drug product in the release testing?	☒	☐	☐
7	Did the Applicant provide complete release data for the test (proposed) drug product (all raw data, range, mean, % CV, date of release testing)?	☒	☐	☐
8	Was the release/release testing and pivotal bioequivalence study conducted using test drug product within the proposed expiry period?	☒	☐	☐
9	Does the proposed product (any strength) have a functional scoring?	☐	☐	☒
10	If there is a functional scoring, did the Applicant provide complete release data for the whole vs. split tablets?	☐	☐	☒
11	Is there significant change in the release of stability samples?	☐	☒	☐

3. REVIEW:

a) List of Submissions being reviewed (table):

10/16/2019	<u>Application 213950 - Sequence 0001 - 0001 (1) 10/16/2019 ORIG-1 /Quality/Presubmission Facility Correspondence</u>
04/15/2020	<u>Application 213950 - Sequence 0006 - 0006 (6) 04/15/2020 ORIG-1 /Multiple Categories/Subcategories</u>
06/22/2020	<u>Application 213950 - Sequence 0008 - 0008 (8) 06/22/2020 ORIG-1 /Multiple Categories/Subcategories</u>

b) Highlight Key Outstanding Issues from Last Review Cycle: The Applicant was requested to revise drug release acceptance criteria.

c) Concise Description of Outstanding Issues: None.

d) In vitro release method and acceptance criteria proposed by the Applicant:

The Applicant has followed the FDA database in vitro release method for Norelgestromin and Ethinyl Estradiol Transdermal System, 150 mcg/35 mcg per day. The proposed release method and acceptance criteria are shown below:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
FDA database method	V – Paddle Over Disk	50	0.1% Hydroxypropyl-Beta-cyclodextrin / 32 ± 0.5°C	900 mL	Norelgestromin: 0.5 hr NM ^{(b) (4)} % 2 hr ^{(b) (4)} % 12 hr NLT ^{(b) (4)} % Ethinyl Estradiol: 0.5 hr NMT ^{(b) (4)} % 2 hr ^{(b) (4)} % 12 hr NLT ^{(b) (4)} %

The Applicant was requested to provide discriminating ability of the in vitro release method (see IR1 in Appendix 1). The Applicant’s response is provided in the document <\\cdsesub1\evsprod\anda213950\0006\m3\32-body-data\32p-drug-prod\ne-ee-tdds-150-35-mcg-01\32p2-pharm-dev\32p2-drug-release-method-development-report.pdf>.

As recommended by the Agency, Applicant conducted studies for formulation variants and process parameters identified as potentially high-risk variables during risk assessments to demonstrate the discriminating ability of the drug release method. (b) (4)

(b) (4)

(b) (4)

e) **In vitro drug release data**

The Applicant provided complete drug release profile data in QC medium for three batches including the bio-batch. The summary and individual data are submitted in document [Dissolution summary and individual data](#) (Page: 28). Batch no#PW-ST-18020A is the bio-batch used in the BE study.

The Applicant's proposed drug release acceptance criteria is as follows:

Norelgestromin:

0.5 hr: NMT $\frac{(b) (4)}{(4)}\%$

2 hr: $\frac{(b) (4)}{(4)}\%$

12 hr: NLT $\frac{(b) (4)}{(4)}\%$

Ethinyl Estradiol:

0.5 hr: NMT $\frac{(b) (4)}{(4)}\%$

2 hr: $\frac{(b) (4)}{(4)}\%$

12 hr: NLT $\frac{(b) (4)}{(4)}\%$

The Applicant's proposed drug release acceptance criteria is wide and not acceptable. Based on the data, the following acceptance criteria is recommended:

Norelgestromin

0.5 hr: $\frac{(b) (4)}{(4)}\%$

2 hr: $\frac{(b) (4)}{(4)}\%$

12 hr: NLT $\frac{(b) (4)}{(4)}\%$

Ethinyl Estradiol

0.5 hr: (b) (4) %

2 hr: (b) (4)

12 hr: NLT (b) (4) %

In response to an IR (see IR2 in Appendix 1), the Applicant has accepted the Agency recommended in vitro release acceptance criteria.

Additional information contained within the submission supporting the proposed release method and acceptance criteria? (i.e. clinical relevance, QbD, etc.)

During formulation development, the Applicant conducted a pilot BE study using batch no. PW-ST-17042A which failed the BE study. The transdermal absorption of Norelgestromin and Ethinyl Estradiol from this batch (b) (4) than that of RS, XULANE®, and did not meet the bioequivalence criterion as the Test/Reference (T/R ratio) geometric mean ratio for C_{max}, AUC(0-t) and AUC(0-inf) were not within the 80-125% limits; they were skewed (b) (4) end for both drugs and (b) (4) limit for EE. (b) (4)

The in vitro release profiles for Ethinyl Estradiol and Norelgestromin were not much different for two Batches # PW-ST-17042A and PW-ST-18020A. This may be because of slight formulation differences between the two batches because the achievement of bioequivalence was accomplished primarily by adjusting the patch size.

REVIEWER'S ASSESSMENT:

In vitro drug release method:

The Applicant has followed FDA database in vitro release method for Norelgestromin and Ethinyl Estradiol Transdermal System. The proposed in vitro release method is acceptable.

Drug release acceptance criteria:

The Applicant's proposed drug release acceptance criteria is wide and not acceptable. Based on the data and per the Agency recommendation, the following acceptance criteria has been accepted by the Applicant:

Norelgestromin

0.5 hr: (b) (4)

2 hr: (b) (4) %

12 hr: NLT (b) (4)

Ethinyl Estradiol

0.5 hr: (b) (4)

2 hr: (b) (4)

12 hr: NLT (b) (4) %

4. CONCLUSION and RECOMMENDATION:

ANDA 213950 is adequate for approval. From Biopharmaceutics perspective, ANDA 213950 is adequate for approval.

Appendix 1

List of Biopharmaceutics Information Requests

Information Request 1 (IR1)

1. Provide data (with appropriate statistics) to support the discriminating ability of your proposed in-vitro drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the drug release profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (b) (4). In addition, if available, submit data showing that the selected method is able to reject batches that are not bioequivalent to the reference batch.

2. Provide the complete drug release profile data [individual (n=12), mean, range, % CV at each time point, and mean profiles] in QC medium for batches PW-ST-18021B and PW-ST-18022B for your proposed drug product in a tabulated form. Also provide the details on manufacturing date, site, size and the drug release test date.

Information Request 2 (IR2)

1. In general, the selection of the in vitro drug release acceptance criteria ranges is based on mean target value (b) (4) for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, etc. Therefore, your proposed in vitro release acceptance criteria are not acceptable.

We recommend the following drug release acceptance criteria based on the submitted data:

Norelgestromin

0.5 hr (b) (4)

2 hr: %



12 hr: NLT $\frac{(b) (4)}{\%}$
Ethinyl Estradiol
0.5 hr: $\frac{(b) (4)}{\%}$
2 hr: $\frac{(b) (4)}{\%}$
12 hr: NLT $\frac{(b) (4)}{\%}$

We request that you acknowledge your acceptance of the recommended acceptance criteria and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period.



Kalpana
Paudel

Digitally signed by Kalpana Paudel

Date: 7/15/2020 12:26:34PM

GUID: 562e1e15002f200f35c6ccac959cdb34



Steven
Yang

Digitally signed by Steven Yang
Date: 8/03/2020 03:01:59PM
GUID: 508da70900028d408c0d8076e85ec0a4



Robert
Berendt

Digitally signed by Robert Berendt
Date: 8/03/2020 03:05:21PM
GUID: 508da7380002b309c612f7e27bdf5995

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

BIOEQUIVLANCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	213950		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System		
Strength(s)	150 µg /35 µg/day		
Applicant Name	Amneal Pharmaceuticals LLC		
Applicant Address	50 Horse Block Road, Brookhaven, NY 11719		
Contact Name and US Mailing Address	Candis Edwards Senior Vice President, Regulatory Affairs Amneal Pharmaceuticals LLC 50 Horseblock Road, Brookhaven, New York 11719, USA E-mail: cedwards@amneal.com		
Contact Telephone Number	631-974-7949		
Contact Fax Number	631-527-3523		
Submission Dates of Original Application and Previous Amendment	12/18/2019 06/12/2020 (BE DRL response)		
Submission Date(s) of Amendment(s) Under Review	08/28/2020 (BE CRL response – Current Amendment)		
Primary Reviewer	Madhusudana Rao Chaluvadi, Ph.D., R.Ph., BCPS		
Secondary Reviewer	Li Xia, Ph.D.		
Tertiary Reviewer	Ke Ren, Ph.D.		
Study Number(s)	ESTN/2018/1607	16-VIN-0236	16-VIN-0235
Study Type(s)	Pivotal Fasting	Pivotal Fasting (Failed)	Pilot Fasting
Strength(s)	150/35 µg/day	150/35 µg/day	150/35 µg/day
Clinical Site (Study No. ESTN/2018/1607)	Synchron Research Services Pvt. Ltd.	Veeda Clinical Research Pvt. Ltd.	
Clinical Site Address	<u>Screening facility:</u> 1 st and 2 nd Floor, Swagat Plaza II, Iscon- Bopal Road, Ambli, Ahmedabad-380 056, Gujarat, India <u>Clinical Study Facility:</u> Clinical Department, 201 & 301, 2 nd & 3 rd Floor, Satva, Opp Bhavin School, Thaltej, Ahmedabad 380059, Gujarat, INDIA	Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India	

Analytical Site	(b) (4)		
Analytical Site Address			
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete	
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☐ Pending ☒ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate ☐ Pending		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date ¹ : May 2009/ Jul 2009, Oct 2016, Oct 2018, Nov 2019 RLD Number: 021180 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 7, 12	Fasting study # ESTN/2018/1607	150/35 µg/day	☒ Adequate ☐ Inadequate

¹ https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

Review of a Study Amendment and a Consult Response

1 EXECUTIVE SUMMARY

This is a review of a bioequivalence (BE) amendment [Supporting Document #12 – Response to Complete Response Letter (CRL), dated 08/28/2020] for Amneal’s ANDA 213950, Norelgestromin (NGMN) and Ethinyl Estradiol (EE) Transdermal System (TDS), 150 µg /35 µg/day and a consult response from the Division of Clinical Review (DCR) regarding evaluation of adequacy of Amneal’s response to the deficiency in CRL whether the difference in proportion of subjects with EE concentrations less than 25 pg/mL at 168 hours (at the time of patch removed) and significant drop of EE concentrations from 72-168 hrs in Amneal’s test product comparing to reference product pose a safety or efficacy concern.

The applicant’s original submission dated 12/18/2019 contained the results of a fasting BE study (No. ESTN/2018/1607) comparing the test product, Amneal’s NGMN and EE TDS, 150 µg /35 µg/day, to the corresponding reference standard (RS), Xulane® (norelgestromin and ethinyl estradiol) 150 µg /35 µg/day TDS (Mylan Technologies, Inc., ANDA 200910). The test and RS products were applied at the abdomen site.

Per the original BE review,² the application was found **inadequate** and the deficiencies were communicated to the applicant through a Division of Bioequivalence III (DBIII)’s Discipline Review Letter (DRL) dated 05/12/2020. In response to DRL, the applicant submitted an amendment on 06/12/2020. Per the BE amendment review,³ the Agency still has a concern on the significant lower concentration of EE observed in the test product at 168 hours, compared to Xulane® in the pivotal fasting BE study (No. ESTN/2018/1607) which may possibly lead to subjects experiencing sub-therapeutic EE level. Therefore, the applicant was requested to provide an explanation along with supportive information for why the difference in EE concentrations is not expected to have an impact on the safety or efficacy of the test product, through a CRL dated 08/16/2020⁴ (please refer to Section 3 for details on background information).

In the current amendment dated 08/28/2020, Amneal submitted its response to the deficiency in the CRL. Amneal pointed out that efficacy of the drug product covers the entire range and duration of wear period for the patch, not just one time point at 168 hrs and supported their point by listing proportion of subjects with EE concentration below 25 pg/mL at each time point from 12 to 168 hrs. Based on the observation that significant proportion of subjects with EE concentrations was below the threshold of 25 pg/mL at all timepoints for the RS Product, and the proportion was also higher than that for the test product except at 144 and 168 hrs, the mean EE concentration for both Test and RS products remain within the therapeutic range of 25 to 75 pg/mL, the range of individual

² GDRP, ANDA-213950-ORIG-1, Bioequivalence Discipline Review, Documents, A213950N000DB-Review01-12182019.docx (<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

³ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>; Document: A213950N000DB-Review02-DRLResponse06122020.pdf

⁴ <https://panorama.fda.gov/task/view?ID=5dfb9847000244072187f7b464d937ac>

observed concentrations of the test formulation at each time point between 72 and 168 hours was basically identical to that of the RS product, and no concentration associated with the test product exceeded the highest reported EE concentration for the RS product, Amneal concludes that the difference in the proportion of subjects who have concentrations below 25 pg/mL at 168 hours is not expected to lead to differences in safety or efficacy between the test and RS products (please refer Section 4.3.1 for details).

To seek the expert opinion on the justifications submitted in the current amendment, on 09/11/2020, the DBIII sent a consult request⁵ to DCR with the questions, whether Amneal's responses provided in 08/28/2020 amendment are sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the RS product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, is not expected to have an impact on the safety or efficacy of the drug product and if there is any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal's test product from 72 to 168 hours comparing to RS Xulane[®]. In addition, if DCR finds a safety concern, DBIII requested DCR's advice on whether PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product. In response⁶ to the consult request, on 12/16/2020, the DCR concludes that the information provided by Amneal on 8/28/2020 is sufficient to support that the observed higher number of subjects in the test group as compared to the reference group with EE concentrations less than 25 pg/mL at time of patch removal (168 hours) and the decrease in EE concentration from 72 hours to 168 hours, which appears to be comparable between products, do not pose a safety or efficacy concern from a clinical perspective. The assessor concurs with DCR's determination on the safety or efficacy of the test product compared to RS and considers the responses submitted in the current amendment are satisfactory (please see details at section 4.4). Therefore, the firm's fasting BE study (No. ESTN/2018/1607) is adequate now.

The applicant also submitted Adhesion study (ESTN/2018/1607) and skin Sensitization/Irritation study (No. GCPAMN002) in the current submission. The DCR reviewed the studies and concluded that irritation potential of the proposed test product is no greater than that of the RS, the sensitization potential of the proposed test product is minimal and adhesion performance of the test product is non-inferior to the RS.⁷

Office of Study Integrity and Surveillance (OSIS) Inspections

Per the Original BE review, OSIS determines that an inspection is not warranted for the Synchron clinical site as the outcome of previous inspections was 'No Action Indicated (NAI)', the OSIS inspection status of the current ANDA is complete. In addition, since the PK endpoint study was conducted at Synchron clinical site, in the original BE review, the assessor conducted further analysis using DABERS tool for overlapping pharmacokinetic (PK) profile and unusual PK trend. Based on DABERS finding, the possible data integrity was not identified.

⁵ <https://panorama.fda.gov/task/view?ID=5f57869300213d87cfd8eaa7ed6519b>

⁶ <https://panorama.fda.gov/task/view?ID=5f57869400213e1619fec71dff47bad3>

⁷ <https://panorama.fda.gov/task/view?ID=5dfb984600023f2b8fd19700df62d564>, Documents: ANDA213950N000DCR Norelgestromin and Ethinyl Estradiol Film.docx

Since the clinical site, Synchron Research Services Pvt. Ltd. was used for PK endpoint study, the assessor further checked the Case Report Forms (CRFs) of the subjects participated in the study. From the thorough evaluation, the assessor could not find any possible data integrity issues for the clinical site and considers the OSIS inspections is complete (Please refer to Section 4.5 for the details).

The application is now **adequate** with no deficiencies.

2 TABLE OF CONTENTS

1	Executive Summary	3
2	Table of Contents	5
3	BACKGROUND INFORMATION	6
4	Submission Summary	11
4.1	Drug Product Information	11
4.2	Contents of Submission	11
4.3	Review of Current Amendment	12
4.3.1	Deficiency #1:	12
4.4	Review of DCR Consult Response	17
4.5	OSIS Status for Clinical Site: Synchron Research Services Pvt. Ltd.	20
4.6	Overall Comments	26
4.7	Attachments	27
4.8	Outcome Page	29

3 BACKGROUND INFORMATION

- In its original application dated 12/18/2019, Amneal Pharmaceuticals LLC submitted the results of a pivotal BE study with pharmacokinetic (PK) endpoints comparing its test product, NGMN and EE TDS, 150 µg /35 µg/day to the corresponding RS, Xulane® (norelgestromin and ethinyl estradiol) 150 µg /35 µg/day TDS (Mylan Technologies, Inc., ANDA 200910). The BE study was designed as a single-dose, two-group, two-way crossover study in healthy non-pregnant, non-lactating female subjects. Since the subjects in the study were dosed in 2 groups, the data was analyzed by the assessor using SAS program with ‘group-by-treatment (TRT*GRP) term’ in the GLM model. The group-by-treatment interactions were found to be insignificant ($p > 0.10$) for all the PK parameters for both NGMN and EE, thus, the assessor dropped TRT*GROUP interaction in the final statistical model. The results are summarized in the tables below.

Ethinyl Estradiol (EE)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1 x 150 µg /35 µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N*	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	6381.51	72	6750.18	72	0.95	90.33	98.95
AUC _∞ (hr *pg/ml)	6459.66	72	6845.92	70**	0.94	90.05	98.87
C _{max} (pg/ml)	46.96	72	46.76	72	1.00	95.91	105.16

* Seven subjects (Nos. (b) (6)) had at least one pre-dose concentration of ethinyl estradiol greater than 5% of their respective C_{max} and were excluded from the PK and statistical analysis.

** (b) (6) were excluded from AUC_i calculation with RS product treatment due to missing the last three and two time-points, respectively and unreliable estimation of elimination rate constant.

Norelgestromin (NGMN)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1x 150 µg /35µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	162429.8	78	160920.3	78	1.01	96.90	105.15
AUC _∞ (hr *pg/ml)	173116.7	78	171855.5	76**	1.01	96.65	104.99
C _{max} (pg/ml)	1029.97	78	1027.76	78	1.00	96.03	104.58

*Subject (b) (6) had pre-dose concentration of norelgestromin greater than 5% of C_{max} with RS product treatment and was excluded from the PK and statistical analysis.

**Subject (b) (6) were excluded from AUC_i calculation due to missing the last three and two time-points with RS product treatment, respectively and unreliable determination of elimination phase.

Based on assessor's calculation, the 90% confidence intervals (CIs) of LnAUC_{0-t}, LnAUC_i and LnC_{max} for both Ethinyl Estradiol and Norelgestromin meet the acceptance criteria of 80.00-125.00%.

Concerns on low loading dose of EE (see details in the original BE review)

- On 03/17/2020, the Office of Pharmaceutical Quality (OPQ) held a meeting with DBIII, Division of Therapeutic Performance (DTP) and DCR to discuss the low loading of EE in Amneal's test patch. Based on residual drug analysis from Mylan's PK study conducted at left or right upper back with overlay, the OPQ team raised a question whether an additional BE study is warranted at non-abdomen site to demonstrate BE of current test product, where approximately 20% higher exposure than the abdomen site is reported. Please note that since overlay was used in Mylan's PK study, the release rate calculated by OPQ based on residual analysis might be overestimated.
- The DBIII discussed about OPQ's concern with the DTP in the ORS in a meeting conducted on 04/08/2020.⁸ DTP raised a concern that the slower release of Amneal's test product from 72-168 hrs compared to RS product might be due to an excessively depleted drug load that might have left an insufficient excess of EE available in the TDS to maintain the concentration gradient and driving force to sustain the same rate and extent of drug delivery as the RS TDS after 72 hours, which may ultimately indicate a sub-optimal initial loading dose of EE and/or a sub-optimal TDS design and/or formulation. In addition, DTP recommended to use modelling approach to address OPQ's concern, so that the generated data could be used as supporting evidence to eliminate the need for another BE study at a non-abdominal site.
- The assessor calculated pAUCs from 0-72 hrs, 0-168 hrs and 72-168 hrs and also did multiple dose/steady state simulation for the application of 3 patches, each patch applied every 168 hrs (7 days). The results indicate that pAUC₀₋₁₆₈ and pAUC₇₂₋₁₆₈ met BE criteria. However, the upper limit of 90% CI (110.08~125.38) for pAUC₀₋₇₂ slightly exceeds the acceptance upper limit of 125.00, with acceptable T/R ratio of 1.18. The results showed a slightly higher exposure for the test product from 0-72 hrs than the RS.
- Per the assessor's multiple dose simulation analysis with nonparametric superposition with application of 3 patches (for 3 weeks), the 90% CIs for AUC_{tau}, AUC_{last} and C_{max} are within the acceptable BE limits, but the lower limit of 90% CI for C_{min} is slightly less than 80% .

Deficiencies in DRL dated 05/12/2020

⁸ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>, Document: A213950N000DB-MeetingMinutes01-04082020.docx

- The original application was **inadequate** due to deficiencies related to bioanalytical method, observed pre-dose concentrations greater than 5% C_{max} for EE and NGMN in period I in some subjects and concerns on low loading dose of EE in the test formulation. The test formulation contains 0.289 mg loading dose of EE, which is only 54.5% of the amount in the RS (0.53 mg loading dose). In the pivotal BE study No. ESTN/2018/1607), the test and RS products were applied on the abdomen. The applicant was asked to provide justification that the loading amount of EE is sufficient when the TDS is applied at other non-abdominal application sites (i.e., buttock, arm, and torso), where the absorption of NGMN and EE is approximately 20% higher than the abdomen site. In addition, the applicant was asked to address the concerns that the slower release observed in the test product may be due to the low loading dose of EE which might result in insufficient excess of drug available within the TDS after 72 hours to maintain the concentration gradient and driving force to sustain the same rate and extent of drug delivery as the RS TDS.
- Prior to conducting the above pivotal BE study (No. ESTN/2018/1607), the applicant conducted a pilot fasting study⁹ (16-VIN-0235, 34 subjects completed for NGMN and 33 subjects completed for EE) and a (failed) pivotal fasting study (16-VIN-0236, 59 subjects completed) with **different** test formulations. The 90% CIs for Ln AUC_t, AUC_i and C_{max} met the BE criteria for NGMN, however, the upper bounds of 90% CIs for all PK parameters are higher than 125.00% for EE in both studies. The applicant applied the transdermal patches at abdomen site in both studies. Due to high EE exposure observed in the failed pilot and 1st pivotal studies, the applicant (b) (6) pilot study to 1st pivotal study (b) (6) and about (b) (6) from 1st pivotal study to the final pivotal study (b) (6) The applicant also decreased the coat weight and increased the concentrations of permeation enhancers as compared to the RS. Due to the issue on loading amount of EE in the test formulation in the final pivotal study (No. ESTN/2018/1607), the applicant was asked to provide the full study reports of the failed pilot and pivotal studies for Agency's further evaluation, and provide composition of test formulations used in these studies, including the quantity in mg/patch for each active and inactive ingredient.
- On 05/12/2020, the aforementioned deficiencies were communicated to the applicant through a DBIII's DRL.¹⁰

Consult request to DQMM

- On 05/16/2020, DBIII sent a consult request¹¹ to the DQMM in ORS to estimate the amount of drug delivered by test TDS on a non-abdominal site (i.e., back) based

⁹ The applicant claimed the fasting study No. 16-VIN-0235 as a pilot study. However, it is considered as a pivotal fasting study based on the subject numbers completed the study.

¹⁰ <https://panorama.fda.gov/task/view?ID=5ebaed240019080bb6ccc71d125b5459>

¹¹ <https://panorama.fda.gov/task/view?ID=5ebab3ac0010e1c8cd8a57fbf4dcef7e>

upon deconvolution of available PK data, and to predict the PK of EE across the back (as a non-abdominal site) based on diffusion parameters obtained for the test product from the abdomen site using a physiologically based model.

- On 07/24/2020, the DQMM sent its response to the consult.¹² In its response, the DQMM concluded that no additional BE study at non-abdomen site is not needed as the Test and the RS products are expected to be bioequivalent following patch application on the back and no EE depletion is expected when the Test product is applied on the back under labeled conditions. Per previous BE amendment review, the assessor agrees with DQMM's conclusion.

Concerns on individual subjects with low EE concentration at 168 hrs

- On 06/12/2020, the applicant submitted an amendment in response to the deficiencies in DRL, sent on 05/12/2020. Per the BE amendment review completed on 08/13/2020,¹³ after reviewing the firm's submitted justifications in the amendment, the Agency still have a concern for lower individual EE concentrations observed for significantly higher number of subjects with test product treatment compared with RS product treatment. Per the assessor's assessment, the EE concentrations for 38.9% (28 subjects) of the total subjects at 168 hours were lower than 25 pg/ml for the test product, compared to 16.7% (12 subjects) of the total subjects for the reference product. This difference in EE concentration between the test and reference products may lead to subjects experiencing sub-therapeutic EE level that may have safety and efficacy concerns for Amneal's test product.
- On 07/30/2020,¹⁴ DBIII met with the Office of Bioequivalence/Immediate Office (OB/IO), the Division of Clinical Review (DCR) and division directors in DB to seek agreement that an additional BE study on non-abdominal site is not necessary based on residual analysis from abdomen PK study and DQMM modeling results, and seek advice if any concern on lower than <25 pg/mL (lowest limit of therapeutic range) of EE concentration at 168 hrs observed in some individual subject for Amneal's test product from efficacy perspective. However, the meeting was inconclusive due to time limitation.
- On 08/04/2020,¹⁵ the DBIII had a follow up meeting with DCR to seek their expert opinion on the concern from efficacy perspective for some individual subjects' concentrations lower than 25 pg/ml and advice on deficiencies if needed, and whether PSG need to be revised to include requirement on minimum concentration level for individual subjects. DCR recommended to send a deficiency to the

¹² <https://panorama.fda.gov/task/view?ID=5ebab3ad0010e1e1a29e7ad274d1c454>

¹³ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c> (A213950N000DB-Review02-DRLResponse06122020.pdf)

¹⁴ A213950N000DB-MeetingMinute01-07302020.docx at <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>

¹⁵ A213950N000DB-MeetingMinute01-08042020.docx at <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>

applicant in this cycle to address this issue, and asked DBIII to send a consult request to DCR when the applicant responds to the deficiency.

- On 08/16/2020, FDA sent a CRL¹⁶ to the applicant requesting them to provide an explanation along with supportive information for why the difference in EE concentrations between the test and RS products at 168 hours is not expected to have an impact on the safety or efficacy of the drug product. However, the assessment team misidentified the deficiency as “minor”, when based on the clinical issue it should have been classified as “major” deficiency.
- On 08/18/2020, the applicant requested for a post CR meeting to clarify the deficiencies noted in the CRL, however, the meeting request was denied because the purpose of a post CR meeting is to clarify the deficiency comments in the CR letter, whereas the applicant provided rationale to address the deficiency in the CR letter. The applicant was asked to submit a post CR amendment.¹⁷
- On 08/28/2020, the applicant submitted its post CR amendment with their response to the deficiency, which is reviewed in Section 4.3.
- On 9/11/2020, DBIII sent a consult request¹⁸ to DCR to seek their expert opinion with the questions, whether Amneal’s responses provided in 08/28/2020 amendment are sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the RS product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, is not expected to have an impact on the safety or efficacy of the drug product and if there is any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal’s test product from 72 to 168 hours comparing to RS Xulane®. After the assessment, if DCR finds a safety concern, DBIII requested DCR’s advice on whether PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product.
- On 09/22/2020,¹⁹ the Office of Generic Drugs (OGD) communicated to the applicant that there are concerns from clinical safety/efficacy perspective on the significantly lower EE concentrations at 168 hours of the test product comparing to RS Xulane®, as the review team identified this information in the 8/28/2020 amendment that requires a substantial expenditure of FDA resources and a change in deficiency classification from ‘minor’ to ‘**major**’ and an adjustment to the goal date to February 27, 2021.

¹⁶ <https://panorama.fda.gov/task/view?ID=5dfb9847000244072187f7b464d937ac>

¹⁷ <https://panorama.fda.gov/task/view?ID=5f3d46f100c0064146d756d8cd9467ca>

¹⁸ <https://panorama.fda.gov/task/view?ID=5f57869300213d87cfdc8eaa7ed6519b>

¹⁹ <https://panorama.fda.gov/task/view?ID=5f6a37f5004ba57d9c52013d2be85ff4>

- On 10/8/2020, the Applicant requested reconsideration on this matter to change it to a minor deficiency based on 6 arguments.²⁰ Besides reiterating the justifications previously submitted in 8/28/2020 amendment, the applicant also provided some new information about PK/PD relationship of EE for the drug product and compared the test product's EE concentrations with the EE concentrations observed in the other marketed products such as NuvaRing, which has lower EE concentrations than current Amneal's product with similar efficacy. On 10/19/2020, the OGD accepted the request²¹ and scheduled a teleconference with Amneal on 10/26/2020. Per Reconsideration Review dated 11/05/2020²², the safety and efficacy issue is still under investigation, pending DCR's consult response. Please note the new information is not evaluated by DCR in the consult response. DCR concluded the firm's response in its 8/28/2020 amendment is adequate (see details at section 4.4).
- On 11/09/2020,²³ the OGD informed the applicant that the August 28, 2020 amendment was reclassified as major during the review because bioequivalence deficiency in the complete response letter (CRL) pertains to an inadequate in vivo bioequivalence study #ESTN/2018/1607 (i.e., there are concerns from clinical safety/efficacy perspective on the significantly lower EE concentrations at 168 hours of their test product comparing to RS Xulane®). The major classification is based on a determination by FDA that the content of the information or data provided in the amendment will require extensive assessment, therefore, the OGD upholds the previous decision regarding 'major' classification and no change will be made to the classification of CRL.
- On 12/16/2020, the DCR submitted its response²⁴ to the consult request, which is reviewed in Section 4.4.

4 SUBMISSION SUMMARY

4.1 Drug Product Information

The drug product, PK/PD information and DB History have not been revised since the completion of original BE review on 05/12/2020 and BE amendment on 08/13/2020.

4.2 Contents of Submission

Study Types	Yes/No?	How many?
BE Studies	No	--
Solubility	No	--

²⁰ <\\CDSESUB1\evsprod\anda213950\0013\m1\us\1-2-cover-letter-esigned-seq-0013-20201008.pdf>

²¹ <https://panorama.fda.gov/task/view?ID=5f807eae0056b2c2aa3551e8fcb35f7d>

²² <https://panorama.fda.gov/task/view?ID=5f807eae0056b2dc40f96583fad77b63>

²³ <https://panorama.fda.gov/task/view?ID=5f807eae0056b3064cc92aae009c13a8>

²⁴ <https://panorama.fda.gov/task/view?ID=5f57869400213e1619fec71dff47bad3>

Permeability	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Failed Studies	No	--
Amendments	Yes	1

4.3 Review of Current Amendment

The applicant's responses (dated 08/28/2020) to the deficiency in CRL (dated 08/16/2020) and the assessor's assessment of those responses are provided in this section of the review.

4.3.1 Deficiency #1:

After reviewing your submitted justifications in the amendment dated 06/12/2020, we still have concern on the significant lower concentration of ethinyl estradiol (EE) in your test product at 168 hours compared to Xulane® in your pivotal fasting BE study (No. ESTN/2018/1607). We acknowledge that based on the inclusion of data from 72 subjects in the pharmacokinetic and statistical analyses the mean concentration for the test product (i.e., 29.5 pg/ml) at 168 hours is within the C_{ss} target range of 25-75 pg/ml of EE for optimum efficacy identified by the innovator of the reference listed drug, Ortho Evra®^[1]. However, the data show that the EE concentrations for 38.9% (28 subjects) of the total subjects at 168 hours were lower than 25 pg/ml for the test product, compared to 16.7% (12 subjects) of the total subjects for the reference product. This difference in EE concentration between the test and reference products may lead to subjects experiencing sub-therapeutic EE levels. The agency requests that you provide an explanation along with supportive information for why the difference in EE concentrations is not expected to have an impact on the safety or efficacy of the drug product.

Applicant's Response to Deficiency #1:

Amneal acknowledges that there is a higher proportion of subjects at 168 hours that have Ethinyl Estradiol (EE) concentrations that are lower than 25 pg/mL for the Test Product versus the Reference Product. Although there is a difference in proportions, Amneal believes that the EE concentrations observed with the Test Product are not expected to have a major safety or efficacy impact and the reasons are described in more detail below.

When examining the proportion of subjects with concentrations below a threshold value, Amneal reviewed the complete profile of both Test and Reference Products and not just

^[1] Drug@FDA (<https://www.accessdata.fda.gov/scripts/cder/daf/>); Search NDA 021180; Clinical Pharmacology Biopharmaceutics Review(s) - https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_biopharmr.pdf

one timepoint because efficacy of the product covers the entire range and duration of wear for the patch. Please refer to **Table 1** for the observed proportion of subjects for both Test and Reference Products with all the timepoints, starting with the 12-hour timepoint.

Table 1. Proportion of Subjects Below 25 pg/mL by Collection Time Points

Timepoint (Hours)	# of subjects with concentration < 25 pg/mL (%)		p-value
	Test (N=72)	Reference (N=72)	
12	55 (76.4%)	67 (93.1%)	0.0401
24	28 (38.9%)	41 (56.9%)	0.0284
36	6 (8.33%)	16 (22.2%)	0.0178
48	5 (6.94%)	15 (20.8%)	0.0148
60	4 (5.56%)	6 (8.33%)	0.2051
72	3 (4.17%)	10 (13.9%)	0.0349
84	3 (4.17%)	8 (11.1%)	0.0806
96	4 (5.56%)	10 (13.9%)	0.0611
120	8 (11.1%)	10 (13.9%)	0.1669
144	18 (25%)	9 (12.5%)	0.0349
168	28 (38.9%)	12 (16.7%)	0.0051

Based on the above result, it is observed that at all timepoints, except for 144 and 168 hours, the proportion of subjects with a concentration lower than 25 pg/ml is higher for the Reference Product than the Test Product. Additionally, if the first 24 hours where concentrations are quickly increasing towards a plateau are excluded, the proportion of subjects with concentrations below 25 pg/mL for the Reference Product remains constant at 8.33 to 16.7% throughout the profile (24 to 168 hours) indicating that a percentage of subjects consistently remain below the threshold of 25 pg/mL for the EE concentrations.

The Reference Product, Xulane[®], was deemed to be safe and efficacious by the FDA, which led to its FDA approval. Considering that for the Reference Product there are significant proportions of subjects below the threshold of 25 pg/mL at all timepoints, the metric “proportion of subjects below 25 pg/mL” may not reflect the relationship to efficacy. Furthermore, considering the significant number of subjects at all timepoints that are below

25 pg/mL for the Reference Product, the individual concentrations below 25 pg/mL appear to be associated with efficacy. Because efficacy and safety are related to exposure, Amneal recommends that instead of comparing the proportion of subjects who have concentrations below 25 pg/mL, it would be more relevant to compare the actual range of concentrations observed for both the test and reference formulations and confirm that the Test Product does not present concentrations that are significantly below those observed with the Reference Product to demonstrate efficacy for the Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day.

Please note the mean EE concentrations for both formulations (T and R) remained above the reported efficacy threshold of 25 pg/mL from the first day up to 168 hours after patch application. Additionally, Amneal did review the individual subject's data to ensure that the Test Product did not present lower concentrations on an individual subject level compared to those observed with the Reference Product, Xulane®.

Individual concentration levels from the Test Product did not fall significantly below what was observed with the Reference Product at the different timepoints. Importantly, individual Test Product values are within the range observed for the Reference Product values throughout the concentration-time profile, as seen in **Table 2**.

Table 2. Range of Concentrations Observed at Time Points 72 to 168 Hours

Timepoint (hours)	Mean (Min; Max) (pg/mL)	
	Reference	Test
72	43.61 (14.15; 84.56)	43.91 (17.13; 89.79)
84	46.09 (15.64; 88.72)	44.6 (16.01; 91.13)
96	43.79 (14.52; 85.58)	40.37 (15.89; 79.79)
120	42.26 (15.22; 92.29)	36.36 (15.20; 69.61)
144	41.63 (15.45; 83.91)	32.91 (15.84; 61.11)
168	41.09 (16.46; 87.49)	29.5 (13.95; 50.26)
Range 72 to 168	14.15 to 92.29	13.95 to 91.13

The lowest observed concentration associated with the Test Product in Amneal's BE study was 13.95 pg/mL, which is basically identical to the lowest observed concentration associated with the reference (14.15 pg/mL). Furthermore, with the exception of one concentration (13.95 pg/mL), all concentrations associated with the Test Product were

greater than the lowest observed concentration for the Reference Product (14.15 pg/mL). Therefore, the range of individual observed concentrations of the test formulation at each time point between 72 and 168 hours were basically identical to the range of observed concentrations for the Reference Product, as demonstrated in the above **Table 2**. Please note that these lower concentrations observed for both formulations in the 72 (associated to approximately Tmax) to 168 hours remain higher than the observed lower concentrations between 24 and 60 hours for the Reference Product as shown in **Table 3**.

Table 3. Range of Concentrations Observed at Time Points 24 to 60 Hours

<i>Timepoint (Hours)</i>	<i>Reference Range (pg/mL)</i>	<i>Test Range (pg/mL)</i>
<i>24 - 60</i>	3.36 to 96.38	9.24 to 94.96

Therefore, based on this information, it is assumed that these individual concentrations (*i.e.*, 72 to 168 hours) are efficacious as they are higher than those observed before 72 hours.

As the Test Product is associated with individual concentrations in the same range as those associated with the Reference Product, the higher proportion of subjects with concentrations lower than 25 pg/mL at 168 hours for the Test Product is not expected to have an impact on the efficacy of the drug product.

Finally, in terms of safety, the previous review of the exposure (*i.e.*, concentrations) is applicable as well. As demonstrated in **Tables 2 and 3**, the mean EE concentration for both Test and Reference Products remain within the therapeutic range of 25 to 75 pg/mL. Additionally, the individual concentrations associated with the Test Product are in the same range as those associated with the Reference Product. Furthermore, no concentration associated with the Test Product exceeded the highest reported EE concentration for the Reference Product. As the Test Product presents concentrations that are in the same range as those observed with the Reference Product and no higher than the highest reported reference concentration, the Test Product is expected to have a similar safety profile as the Reference Product.

CONCLUSION

The Mean concentrations of EE starting at 24 hours for both the Test and Reference Products were within the target range of 25 to 75 pg/mL which are associated with efficacy and safety. Furthermore, the individual EE concentration range between 72 (approximately Tmax) and 168 hours for the Test and Reference Products were basically the same between products. Therefore, the difference in the proportion of subjects who have concentrations below 25 pg/mL at 168 hours is not expected to lead to differences in safety or efficacy between the Test and Reference Products.

Finally, please note the Test Product met the BE criteria and the concern raised by the FDA it is not expected to impact efficacy and safety for the consumer and is deemed bioequivalent to the Reference Product.

Assessor's Comments on Applicant's Response to Deficiency #1:

- Amneal acknowledges that there is a higher proportion of subjects at 168 hours with EE concentrations lower than 25 pg/mL for the Test Product compared to the RS Product. The applicant pointed out that efficacy of the drug product covers the entire range and duration of wear period for the patch, not just one time point (i.e. at 168 hrs, patch removal).
- Amneal listed proportion of subjects with EE concentration below 25 pg/mL at each time point from 12 to 168 hrs (Table 1 above) and stated that it is observed that at all timepoints, except for 144 and 168 hours, the proportion of subjects with a concentration lower than 25 pg/ml is higher for the RS Product than the Test Product.
- Additionally, considering there are significant proportion of subjects below the threshold of 25 pg/mL at all timepoints for the RS Product, per Amneal, the metric “proportion of subjects below 25 pg/mL” may not reflect the relationship to efficacy. Because efficacy and safety are related to exposure, and Amneal believes it would be more relevant to compare the actual range of individual concentrations observed for both the test and RS formulations rather than comparing the subjects with concentrations less than 25 pg/ml at 168 hrs.
- Further, Amneal listed mean Test and RS Product concentrations with range (min, max) from 72 hrs to 168 hrs (Table 2 above) and states that the range of individual observed concentrations of the test formulation at each time point between 72 and 168 hours (13.95 to 91.13 pg/mL) was basically identical to that of the RS Product (14.15 to 92.29 pg/mL).
- Amneal also states that the lower concentrations observed for both formulations from 72 (associated to approximately Tmax) to 168 hours remain higher than the lower concentrations (range: 3.36 to 96.38 pg/ml) between 24 and 60 hours for the RS Product. Therefore, it is assumed that these individual concentrations (i.e., 72 to 168 hours) are efficacious as they are higher than those observed before 72 hours.
- In terms of safety, Amneal deems the mean EE concentration for both Test and RS Products remain within the therapeutic range of 25 to 75 pg/mL. Additionally, the individual concentrations associated with the Test Product are in the same range as those associated with the RS Product, and no concentration associated with the Test Product exceeded the highest reported EE concentration for the RS Product, so the Test Product is expected to have a similar safety profile as the RS Product.
- From the above justifications, Amneal concludes that the difference in the proportion of subjects who have concentrations below 25 pg/mL at 168 hours is not expected to lead to differences in safety or efficacy between the Test and RS Products.

- Based on the clinical nature of the justifications provided by the applicant, the concerns from a clinical safety/efficacy perspective still remain on the significantly lower EE concentrations at 168 hours (at the time of patch removal) of the test product comparing to RS Xulane[®]. Therefore, the applicant's response to Deficiency #1 needs expert evaluation with respect to clinical safety/efficacy perspective.
- A consult request was sent to DCR regarding this issue, and DCR in its consult response concluded that the information provided by the applicant on 08/28/2020 is adequate, and the differences in EE concentrations less than 25 pg/mL from 72 hours to 168 hours (at the time of patch removal) observed in a single dose PK study pose no safety or efficacy concern from a clinical perspective (please refer to the details in the next section, Section 4.4). The assessor concurs with the DCR's determination, therefore, Amneal's response to Deficiency #1 is **adequate**.

4.4 Review of DCR Consult Response

- To seek expert opinion with the applicant's CRL response regarding safety and efficacy concerns on EE difference between test and reference products, DBIII sent a formal consult request to DCR on 09/11/2020²⁵ for the following three questions:

1) Are Amneal's justifications provided in its 08/28 amendment sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the RS (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, i.e. at the time of patch removal, is not expected to have an impact on the safety or efficacy of the drug product?

2) Is there any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal's test product from 72 to 168 hours compared to RS Xulane[®]?

3) If the answer is 'yes', to the above questions, we seek your advice on whether the PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product.

- On 12/16/2020, the DCR responded with their responses to the consult request.²⁶ In addition to the documents submitted as part of DB III's consult request, DCR reviewed the regulatory background of the current drug product, pending ANDAs of the current drug product, Controlled Correspondences relevant to the current review, RLD Drug Product Label dated 08/2017, current PSG on NGMN and EE TDS and RLD studies relevant to the questions in current consult request, which are summarized below.

²⁵ <https://panorama.fda.gov/task/view?ID=5f57869300213d87cfdc8eaa7ed6519b>

²⁶ <https://panorama.fda.gov/task/view?ID=5f57869400213e1619fec71dff47bad3>

- **DCR's response to Questions 1 and 2:**

DCR concludes that Amneal's justifications provided in Amendment-12 dated 08/28/2020 are adequate. Although a higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentrations less than 25 pg/ml at 168 hours (just prior to patch removal) was observed, and the EE concentrations appear to rapidly decrease from 72 to 168 hours in Amneal's product compared to that of Xulane, the difference in individual subjects' EE concentrations is not expected to have an impact on the safety or efficacy of the drug product for the following reasons:

1. Both the test product and the RS were determined to be bioequivalent based on PK profile comparison in a single dose BE study (No. ESTN/2018/1607) by DB III which used mean EE concentrations for determination of BE between products. RS shows higher variability in AUC₀₋₂₄₀ evidenced by higher %CV and wider range compared to the test product, which has maintained the release rate of EE with lesser variability. pAUCs from 0-168 and 72-168 hours between products were shown to be within acceptable BE criteria. Based on the DBIII assessment, the proposed test formulation was acceptable.
2. According to the RLD label (Ortho Evra), in one of the clinical studies, the C_{ss} concentrations across all subjects ranged from 23 to 137 pg/mL for EE. Per Clinical Pharmacology review dated 11/19/2001 for the approval of the RLD (NDA 021180), the reviewer noted that the optimum efficacy C_{ss} target concentrations of EE identified by the NDA sponsor was 25-75 pg/mL. However, in one NDA study (No. NRGTRI-OC-115), following oral administration of Ortho Tri-Cyclen for three cycles had the mean C_{min} of EE concentrations observed on Day 7 (i.e., 168 hour) as 21.9 pg/mL and on Day 14 was 21.1 pg/mL, which were lower than the optimum efficacy concentrations. Per RLD label, the EE PK profile for the Ortho Evra patch has a higher C_{ss} and a lower C_{max} compared to oral ethinyl estradiol administration. In another study (No. NRGEEP-PHI-013), following the application of ORTHO EVRA in healthy female volunteers on the buttock for three consecutive cycles, the mean EE concentrations during the first cycle of patch wear (cycle 1, week 1), show a decrease in EE concentration starting at 72 hours and reach a plateau by 120 hours until 168 hours. In another study (No. NRGEEP-PHI-004), some patients showed EE steady-state serum levels below the target range from a single application at abdomen site as well as at torso site, but for this test product, the mean C_{ss} EE concentrations were all within target range of 25 pg/mL to 75 ug/mL at all time points including at 168 hours.
3. According to the Applicant's analysis provided as response in amendment dated 08/28/20, up to 93.1% subjects in the reference group had less than 25 pg/mL of EE compared to 76.4% in the test group at 12 hours. At 48 hours

(close to Cmax), up to 20.8% subjects in the reference group had less than 25 pg/mL of EE compared to 6.94% in the test group. Except for 144 and 168 hours, all other time points had significantly higher proportions of subjects who had EE concentrations below 25 pg/mL in the reference group compared to that in the test group.

4. At the time of patch removal (i.e., 168 hours), the mean EE concentration in the test group was 29.5 pg/mL which was above 25 pg/mL and individual EE concentrations ranged from 13.95 to 50.26 pg/mL. In the reference group, the mean EE concentration was 41.09 pg/mL and ranged from 16.46 to 87.49 pg/mL. Based on the applicant's analysis result, some individual EE concentrations fell below the 25 pg/mL at all time points during the first 7-day patch application within the reference group. The test product had the lowest EE concentration of 13.95 pg/mL at 168 hours compared to 16.46 pg/mL in reference group, but the mean EE concentration was above 25 pg/mL (i.e., 29.5 pg/mL).
5. Per the applicant, EE concentrations ranged from 13.95 to 91.13 pg/mL in the test group compared to 14.15 to 92.29 pg/mL in the reference group from 72 hours to 168 hours. The mean concentrations of EE were comparable between test and reference groups at times 72, 84, 96, 120, and 144 hours. The greatest difference in mean EE concentration between products was at 168 hours (41.09 pg/mL in RS vs. 29.5 pg/mL in test). Considering that the mean of EE concentrations was maintained steady and comparable between products from 72 hours to 144 hours, DCR does not consider that there is a sudden decrease in EE concentrations. Again at 168 hours prior to patch removal, the difference in mean EE concentrations observed is not considered clinically meaningful when the mean EE concentrations in both products were above 25 pg/mL. According to the RLD label, a woman can start using Ortho Evra TDS during the first 24 hours of her menstrual period or on the first Sunday after her menstrual period begins. Those who choose to start on the first Sunday after the menstrual period begins are recommended to use a non-hormonal backup method of birth control such as a condom and spermicide or diaphragm and spermicide to prevent unwanted pregnancy for the first 7 days of the first cycle. Therefore, the individual EE concentration differences observed at 168 hours on the first cycle between products do not appear to be a safety or efficacy concern from a clinical perspective since this drug product is indicated for chronic use and users are supposed to have two additional cycles of patch application for a total of 3 cycles every month.
6. Although an optimum range of EE concentrations of 25 pg/mL to 75 pg/mL is noted by the NDA sponsor, DCR is not aware of any other oral or topical patch contraceptives containing EE requiring minimum therapeutic levels, when there is no clear minimum efficacy concentration known for EE in these products.

7. The RLD studies were evaluated based on mean pharmacokinetic parameters, not individual EE concentrations

- **DCR's response to Questions 3:**

From DCR's perspective, the difference in proportion of subjects with EE concentrations less than 25 pg/mL at 168 hours does not appear to be a safety or efficacy concern to require a minimum concentration of EE level at the time of patch removal at 168 hours for this drug product.

Based on the information provided in Amendment-12, DCR agrees with the applicant that there is no safety or efficacy concern related to reported lower EE concentrations at 168 hours in the test product compared to that in the RS. Thus, for question 3, DCR does not consider that the PSG should be revised based on findings from the current PK study.

- **DCR's Conclusion:**

DCR concludes that the information provided by the Applicant on 8/28/2020 is sufficient to support that the observed higher number of subjects in the test group as compared to the reference group with EE concentrations less than 25 pg/mL at time of patch removal (168 hours) and the decrease in EE concentration from 72 hours to 168 hours, which appears to be comparable between products, do not pose a safety or efficacy concern from a clinical perspective.

4.5 OSIS Status for Clinical Site: Synchron Research Services Pvt. Ltd.

Since the PK endpoint study was conducted at Synchron clinical site, in the original BE review, the assessor conducted further analysis using DABERS tool for similar PK profile and unusual PK trend . Based on DABERS finding, possible data integrity issue was not identified.

However, possible data integrity issues were identified in the some other ANDAs (e.g. ^{(b) (4)} using Synchron as the clinical site due to several subjects with same birth date, height and body weight. In addition, Synchron Research Services Pvt. Ltd. is under further evaluation by Data Integrity Work_Group within Office of Bioequivalence/OGD and OSIS. Therefore, the assessor further evaluated clinical study in the current application to find out any possible data integrity issues.

To find out any data integrity issues at Synchron clinical site with respect to questions raised by Data Integrity Work_Group, the assessor identified the study subjects with January 1st as the Date of Birth (DOB), checked whether the study subjects having same height and weight. The assessor also compared this information to other clinical sites in India to find out whether January 1st DOB and duplicate DOBs are common in Indian

^{(b) (4)}

clinical sites, and compared this activity to some clinical sites in USA/Canada. In addition, the assessor went through some case report forms (CRFs) to find out any crossing/strike outs in the CRFs in the current clinical study.

Synchron Clinical Site: Duplicate DOBs

DOB	Frequency
MISSING (b) (6)	9
[REDACTED]	3
	2
	2
	3

Height and Weight details of Subjects with duplicate DOBs

Sl. No.	Subject ID	DOB (b) (6)	Height (meters)	Weight (Kg)
1	[REDACTED]	[REDACTED]	1.46	53.1
2			1.53	57.1
3			1.535	63.4
4			1.49	55.4
5			1.46	51.7
6			1.52	53.2
7			1.48	52.5
8			1.43	53.2
9			1.54	65.4
10			1.51	68.0

Assessor’s Comments: From the above tables, there are 9 subjects with missing DOBs. The applicant did not provide any reason for missing DOBs, however, the assessor doesn’t think it as suspicious activity as different age, height, weight and other demographics are provided in the CRFs. From the above tables, there are 10 subjects with same DOBs (duplicate and triplicate) for 4 sets of DOBs [REDACTED] (b) (6). Among them [REDACTED] (b) (6) is common DOB for eight subjects, however, as noted above, the heights and weights are different for the subjects with duplicate DOBs.

To find out whether the [REDACTED] (b) (6) DOBs and duplicate DOBs for these 10 subjects is a data integrity issue, the assessor evaluated other clinical sites in India and some clinical sites in the USA/Canada.

Clinical Sites in India, USA and Canada with DOB as January 1st and duplicate DOBs in comparison to Synchron clinical site in current ANDA 213950

India

DOB	Frequency						
	Synchron, A213950	Accutest, A213112	Actimus, A213891	Alkem, A213613	Apotex, A213159	Axis Clinicals, A213662	Axis Clinicals, A214473
MISSING (b) (6)	9	--	--	--	--	--	--
	--	1	--	--	--	--	1
	--	1	--	--	1	--	--
	--	1	--	--	1	--	--
	--	--	1	--	--	--	--
	--	--	--	--	1	1	--
	--	2	1	--	1	--	--
	--	--	--	--	2	--	--
	--	1	--	1	2	--	--
	--	--	--	--	1	--	--
	--	1	1	--	--	2	2
	--	1	--	--	1	--	--
	3	--	--	--	1	--	--
	--	--	--	--	2	--	--
	2	--	--	1	1	--	--
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India, Cont...

DOB	Frequency							
	Axis Clinicals, A212567	Azidus A213427	Azidus A215259	Jamia Hamdard A211707	(b) (4)	Sun Pharma A213447	Veeda Clinical A212948	Watson A215506
MISSING (b) (6)	--	--	--	--	--	--	--	--
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(b) (6)

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(b) (6)	2	--	--	--	--	--	--	--
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USA and Canada

Out of 4 Clinical sites verified from Canada (Syneos Health, A215012) and USA (Bio-Kinetic, A209263; Novum Pharma, A211271; and Watson, A213977), there were no duplicate DOBs. Also, there was only 1 subject with January 1st as DOB (01/01/1979 from ANDA 209263)

Assessor’s Comments: From the above data analysis in the tables, all other clinical sites checked from other ANDAs in India have similar DOB distribution with considerable number of subjects having January 1st as DOB and duplicate DOBs, especially with January 1st DOB similar to the pattern at Synchron Clinical site in the current application. However, the four clinical sites in the USA and Canada have a different pattern DOBs with no duplicate DOBs and only have one subject with January 1st as DOB. The assessor assumes that due to some low socioeconomic status of the study subjects in India, accuracy of DOBs in records maybe a common issue but not specific to Synchron Clinical site. Therefore, the DOB pattern is not considered as a data integrity issue.

In addition, the assessor browsed approximately 20 CRFs (~1/4th of the study subjects), but could only find one strike out/crossing (Subject (b) (6) on date of birth, which is not a concern as strike out happened only once.

Per the original BE review, OSIS determines that an inspection is not warranted for the Synchron Clinical site²⁸ as the outcome of previous inspections was ‘No Action Indicated (NAI)’. The Office of Regulatory Affairs (ORA) inspected the site in June 2018 under ANDA 211293. For current ANDA 213950, the pivotal in vivo BE study (No. ESTN/2018/1607) was conducted in March~ April 2019, which fell within the surveillance interval. Furthermore, the assessor looked at the history of this clinical site regarding OSIS inspection and the results are presented below.

- 11/12/2019: OSIS declined to inspect clinic site
- 01/14/2020: OSIS declined inspect per current ANDA
- 01/27/2020: inspect MES/2017/1385 (ANDA (b) (4)) and DIL/2016/1354 (ANDA 213193)
 - 485 issued

²⁸ GDRP, ANDA-213950-ORIG-1, Clinical PK/PD Sites, Site: SYNCHRON RESEARCH SERVICES PVT LTD, Decline to Inspect_A213950_Synchron_Research_Clin.Pdf, archived on 1/14/19 (<https://panorama.fda.gov/task/view?ID=5dfd477e005813c17105d93835539524>)

- Voluntary Action Indicated (VAI) (details below)
- 04/10/2020 amend EIR by adding analytical information (ANDA (b) (4)): VAI (details below)
- 04/13/2020: for-cause for (b) (4): NAI (details below)

From the OSIS inspection from studies (b) (4) (ANDA (b) (4)) and (b) (4), the EIR dated (b) (4) a Form 483 was issued as the inspection outcome resulted in VAI. The OSIS findings were the clinical study site personnel are not practicing good clinical practices regarding X-rays were not available or not properly identified for both ANDAs, For ANDA (b) (4) ECHO images were unavailable for 57 enrolled subjects, For ANDA (b) (4) compliance with the dosing requirement could not be verified, and For ANDA (b) (4) pharmacokinetic sample accountability records were not adequate and accurate. After the review of applicant's response to the above findings, the OSIS concluded that the objectionable conditions did not impact the reliability of the data from the audited studies and the overall performance of the site was adequate and is unlikely to impact the integrity of the data from other studies of similar design. The above observations were not related to the current study as such findings were not observed in the current study.

Regarding the amend EIR by adding analytical information (ANDA 213734) from (b) (4) This is an amendment to the above EIR dated (b) (4) where OSIS later found data integrity issues from the analytical portions of the same studies (ANDA (b) (4) (b) (4)), conducted in (b) (4) having several concerning issues which may compromise the reliability of all study data generated at (b) (4) Specifically, the concentration-time profiles overlapped for some subjects in the audited studies and the analytical portion of studies were considered 'VAI'. As per the original review of current ANDA, based on DABERS finding, the possible data integrity was not identified for the current application. Therefore, the finding in this VAI are not applicable to the current application.

Regarding the for-cause inspection from 04/13/2020:³¹ Synchron has two clinical sites (Ambli, FEI # 3007240297) and Satva (FEI #3011994794)) (b) (4) (b) (4) The for-cause clinical inspection was conducted at the Satva site. The inspection was conducted because OB is concerned with anomalies in the pharmacokinetic (PK) data from study (b) (4) under ANDA (b) (4). Specifically, OGD noticed significant group effects in the two study cohorts and there is concern that investigational drug products (test or reference) and/or study samples maybe have been switched to influence the bioequivalence endpoint of the study. In addition, the concentration-time profiles overlap for several study subjects.

(b) (4)

³⁰ <https://panorama.fda.gov/task/view?ID=5de94481003d4d1cef7fdd856e502b80>

³¹ <https://panorama.fda.gov/task/view?ID=5d5ad98a000d4de236f8cd593f0d7b01>

The inspection of Synchron Satva did not identify possible causes for the PK anomalies described above. No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out. The final inspection classification for Synchron Satva is No Action Indicated (NAI).

For the current application (ANDA 213950), the screening was conducted at Ambli site and clinical study was conducted at Satva site. Per the original review of current ANDA, there is no significant group effect in the pivotal BE study (No. ESTN/2018/1607), and based on DABERS finding, there are no PK profile overlapping and unusual T/R ratio trend observed in the study. The assessor also checked if there were any anomalies in CRF and analytical results including checking the order of sample analysis for potential clinical and analytical issues, but could not find any suspicious data, so possible data integrity was not identified for the current application. Therefore, the for cause inspection results are not applicable to the current application.

Therefore, after thorough evaluation, the assessor could not find any data integrity issues from the history and in the current study in the current application and considers the OSIS inspections is complete for the Clinical site.

4.6 Overall Comments

- The assessor concurs with DCR's evaluation and final determination that the difference in proportion of subjects with EE concentrations less than 25 pg/mL at 168 hour is not a safety or efficacy concern to require a minimum concentration of EE level at the time of patch removal (i.e., 168 hour) for this drug product, and the drop in EE concentrations in Amneal's test product from 72 hours to 168 hours (at time of patch removal) observed in a single dose PK study poses no safety or efficacy concern from a clinical perspective. Therefore, the applicant's responses submitted in the current amendment are satisfactory.
- In addition, the OSIS inspection is complete for both clinical and analytical sites.
- The application is now **adequate** with no deficiencies.

4.7 Attachments

- Consult Request to DCR³²



A213950N000DB-Co
nsultRequest01-DCF

- Consult Response from DCR³³



A213950 Clin_
Norelgestromin and

- MEMORANDUM TO FILE-Request for Reconsideration (RFR) Response³⁴



A213950N000DB-Re
sponse01-Reconsid

³² <https://panorama.fda.gov/task/view?ID=5f57869300213d87cfd8eaa7ed6519b>

³³ <https://panorama.fda.gov/task/view?ID=5f57869400213e1619fec71dff47bad3>

³⁴ <https://panorama.fda.gov/task/view?ID=5f807eae0056b2dc40f96583fad77b63>

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 213950
APPLICANT: Amneal Pharmaceuticals LLC
DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System,
150 µg/35 µg/day

The Division of Bioequivalence III (DBIII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

Completed Assignment for 213950 ID: 44173

Assessor: Madhusudana Rao Chaluvadi

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Norelgestromin and Ethinyl Estradiol
Transdermal System, 150/35 µg

Items:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
44173	08/28/2020	BIO	ANDA Amendment [1]	1	1
44173	08/28/2020	BIO	Consult Review (For Consults to Other Office) [1]	1	1
44173	08/28/2020	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
44173	08/28/2020	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	4.5

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	213950-ORIG-1
Product Name	Norelgestromin (NG) and Ethinyl Estradiol (EE) Transdermal System, 150 mcg/35 mcg per day
Applicant	Amneal Pharmaceuticals LLC
Dosage Form/Strengths	Transdermal Delivery System (TDS)/ 150 mcg/35 mcg per day
Route of Administration	Transdermal
Indication for Use	Estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch.
RLD/RS	RLD: Ortho Evra® (norelgestromin and ethinyl estradiol) TDS, 150 µg /35 µg/day RS: Xulane® (norelgestromin and ethinyl estradiol), 150 µg /35 mcg/day TDS
Submission Date	Original:10/16/2019 IR response: 04/15/2020 IR response: 06/22/2020
Review Date	03/05/2020; 05/26/2020; 07/14/2020
Primary Reviewer	Kalpana Paudel, Ph.D.
Secondary Reviewer	NA
Recommendation	ADEQUATE

1. REVIEW SUMMARY:

Background:

The proposed drug product, Norelgestromin (NG) and Ethinyl Estradiol (EE) Transdermal System, 150 mcg/35 mcg per day, is a generic product of the reference listed drug (RLD) Ortho Evra®, 150 mcg/35 mcg per day by Janssen Pharmaceuticals, Inc. under NDA# 021180. However, since Ortho Evra® has been withdrawn from sale for reasons other than safety and efficacy, the Applicant used the reference standard selected by the FDA, Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System), 150 mcg/35 mcg per day by Mylan Technologies, Inc. under ANDA 200910 for in vivo bioequivalence studies.

Submission:

The Applicant has submitted the in vitro drug release method, the drug release data for the proposed drug product and the RLD and proposed drug release acceptance criteria as the quality control (QC) tool.

Review's Objective:

The review is focused on evaluation of the proposed in vitro drug release method and acceptance criteria.

Reviewer's Assessment:

The following in vitro drug release method and acceptance criteria are approved:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
FDA database method	V – Paddle Over Disk	50	0.1% Hydroxypropyl-Beta-cyclodextrin / 32 ± 0.5°C	900 mL	Norelgestromin 0.5 hr: (b) (4) 2 hr: (b) (4) % 12 hr: NLT (b) (4) % Ethinyl Estradiol 0.5 hr: (b) (4) 2 hr: (b) (4) 12 hr: NLT (b) (4) %

Conclusion and Recommendation:

From Biopharmaceutics perspective, ANDA 213950 is adequate for approval.

2. SUBMISSION CONTENT CHECKLIST:

INFORMATION		YES	NO	N/A
1	Is there a USP release method?	☐	☒	☐
2	Did the Applicant use the USP release method?	☐	☐	☒
3	Is there an FDA-Database release method?	☒	☐	☐
4	Did the Applicant use the FDA-Database release method?	☒	☐	☐
5	Did the Applicant conduct release testing with a proposed in-house release method?	☐	☒	☐
6	Did the Applicant use 12 individual units of the test (proposed) drug product in the release testing?	☒	☐	☐
7	Did the Applicant provide complete release data for the test (proposed) drug product (all raw data, range, mean, % CV, date of release testing)?	☒	☐	☐
8	Was the release/release testing and pivotal bioequivalence study conducted using test drug product within the proposed expiry period?	☒	☐	☐
9	Does the proposed product (any strength) have a functional scoring?	☐	☐	☒
10	If there is a functional scoring, did the Applicant provide complete release data for the whole vs. split tablets?	☐	☐	☒
11	Is there significant change in the release of stability samples?	☐	☒	☐

3. REVIEW:

a) List of Submissions being reviewed (table):

10/16/2019	<u>Application 213950 - Sequence 0001 - 0001 (1) 10/16/2019 ORIG-1 /Quality/Presubmission Facility Correspondence</u>
04/15/2020	<u>Application 213950 - Sequence 0006 - 0006 (6) 04/15/2020 ORIG-1 /Multiple Categories/Subcategories</u>
06/22/2020	<u>Application 213950 - Sequence 0008 - 0008 (8) 06/22/2020 ORIG-1 /Multiple Categories/Subcategories</u>

b) Highlight Key Outstanding Issues from Last Review Cycle: The Applicant was requested to revise drug release acceptance criteria.

c) Concise Description of Outstanding Issues: None.

d) In vitro release method and acceptance criteria proposed by the Applicant:

The Applicant has followed the FDA database in vitro release method for Norelgestromin and Ethinyl Estradiol Transdermal System, 150 mcg/35 mcg per day. The proposed release method and acceptance criteria are shown below:

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance criteria
FDA database method	V – Paddle Over Disk	50	0.1% Hydroxypropyl-Beta-cyclodextrin / 32 ± 0.5°C	900 mL	Norelgestromin: 0.5 hr NMT $\frac{(b)(4)}{100}\%$ 2 hr $\frac{(b)(4)}{100}\%$ 12 hr NLT $\frac{(b)(4)}{100}\%$ Ethinyl Estradiol: 0.5 hr NMT $\frac{(b)(4)}{100}\%$ 2 hr $\frac{(b)(4)}{100}\%$ 12 hr NLT $\frac{(b)(4)}{100}\%$

The Applicant was requested to provide discriminating ability of the in vitro release method (see IR1 in Appendix 1). The Applicant’s response is provided in the document <\\cdsesub1\evsprod\anda213950\0006\m3\32-body-data\32p-drug-prod\ne-ee-tdds-150-35-mcg-01\32p2-pharm-dev\32p2-drug-release-method-development-report.pdf>.

As recommended by the Agency, Applicant conducted studies for formulation variants and process parameters identified (b) (4)



However, it is still controlled with the specification ranges.

(b) (4)

The Applicant also investigated the drug release after one day or seven days following coating which are similar, thus not needing any equilibration time prior to the conduct of drug release testing.

e) **In vitro drug release data**

The Applicant provided complete drug release profile data in QC medium for three batches including the bio-batch. The summary and individual data are submitted in document [Dissolution summary and individual data](#) (Page: 28). Batch no#PW-ST-18020A is the bio-batch used in the BE study.

The Applicant's proposed drug release acceptance criteria is as follows:

Norelgestromin:
0.5 hr: NMT (b) (4)
2 hr: (b) (4) %
12 hr: NLT (b) (4) %

Ethinyl Estradiol:
0.5 hr: NMT (b) (4) %
2 hr: (b) (4) %
12 hr: NLT (b) (4) %

The Applicant's proposed drug release acceptance criteria is wide and not acceptable. Based on the data, the following acceptance criteria is recommended:

Norelgestromin
0.5 hr: (b) (4)
2 hr: (b) (4) %
12 hr: NLT (b) (4) %

Ethinyl Estradiol

0.5 hr: (b) (4)

2 hr: (b) (4)

12 hr: NLT (b) (4) %

In response to an IR (see IR2 in Appendix 1), the Applicant has accepted the Agency recommended in vitro release acceptance criteria.

Additional information contained within the submission supporting the proposed release method and acceptance criteria? (i.e. clinical relevance, QbD, etc.)

During formulation development, the Applicant conducted a pilot BE study using batch no. PW-ST-17042A which failed the BE study. The transdermal absorption of Norelgestromin and Ethinyl Estradiol from this batch was higher than that of RS, XULANE®, and did not meet the bioequivalence criterion as the Test/Reference (T/R ratio) geometric mean ratio for C_{max}, AUC(0-t) and AUC(0-inf) were not within the 80-125% limits; (b) (4)

(b) (4)

(b) (4)

(b) (4) Batch # PW-ST-18020A in order to achieve bioequivalence.

The in vitro release profiles for Ethinyl Estradiol and Norelgestromin were not much different for two Batches # PW-ST-17042A and PW-ST-18020A. This may be because of slight formulation differences between the two batches because the achievement of bioequivalence was accomplished primarily by adjusting the patch size.

REVIEWER'S ASSESSMENT:

In vitro drug release method:

The Applicant has followed FDA database in vitro release method for Norelgestromin and Ethinyl Estradiol Transdermal System. The proposed in vitro release method is acceptable.

Drug release acceptance criteria:

The Applicant's proposed drug release acceptance criteria is wide and not acceptable. Based on the data and per the Agency recommendation, the following acceptance criteria has been accepted by the Applicant:

Norelgestromin

0.5 hr: (b) (4)

2 hr: (b) (4) %

12 hr: NLT (b) (4) %

Ethinyl Estradiol

0.5 hr: (b) (4) %

2 hr: (b) (4) %

12 hr: NLT (b) (4) %

4. CONCLUSION and RECOMMENDATION:

ANDA 213950 is adequate for approval. From Biopharmaceutics perspective, ANDA 213950 is adequate for approval.

Appendix 1

List of Biopharmaceutics Information Requests

Information Request 1 (IR1)

1. Provide data (with appropriate statistics) to support the discriminating ability of your proposed in-vitro drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the drug release profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10 -20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected method is able to reject batches that are not bioequivalent to the reference batch.

2. Provide the complete drug release profile data [individual (n=12), mean, range, % CV at each time point, and mean profiles] in QC medium for batches PW-ST-18021B and PW-ST-18022B for your proposed drug product in a tabulated form. Also provide the details on manufacturing date, site, size and the drug release test date.

Information Request 2 (IR2)

1. In general, the selection of the in vitro drug release acceptance criteria ranges is based on mean target value (b) (4) % for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an approved IVIVC model, physiologically based absorption and pharmacokinetic model, etc. Therefore, your proposed in vitro release acceptance criteria are not acceptable.

We recommend the following drug release acceptance criteria based on the submitted data:

Norelgestromin

0.5 hr: (b) (4)

2 hr: %



12 hr: NLT (b)(4)%

Ethinyl Estradiol

0.5 hr: (b)(4)%

2 hr:

12 hr: NLT (b)(4)%

We request that you acknowledge your acceptance of the recommended acceptance criteria and update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet the revised dissolution specification in your stability program through your proposed expiry period.



Kalpana
Paudel

Digitally signed by Kalpana Paudel

Date: 7/15/2020 12:26:34PM

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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	213950		
Drug Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System		
Strength(s)	150 µg /35 µg/day		
Applicant Name	Amneal Pharmaceuticals LLC		
Applicant Address	50 Horse Block Road, Brookhaven, NY 11719		
Contact Name and US Mailing Address	Candis Edwards Senior Vice President, Regulatory Affairs Amneal Pharmaceuticals LLC 50 Horseblock Road, Brookhaven, New York 11719, USA E-mail: cedwards@amneal.com		
Contact Telephone Number	631-974-7949		
Contact Fax Number	631-527-3523		
Original Submission Date(s)	12/18/2019		
Submission Date(s) of Amendment(s) Under Review	N/A		
Primary Reviewer	Madhusudana Rao Chaluvadi, Ph.D., R.Ph., BCPS		
Secondary Reviewer	Li Xia, Ph.D.		
Tertiary Reviewer	Ke Ren, Ph.D.		
Study Number(s)	ESTN/2018/1607	16-VIN-0236	16-VIN-0235
Study Type(s)	Pivotal Fasting	Pivotal Fasting (Failed)	Pilot Fasting
Strength(s)	150/35 µg/day	150/35 µg/day	150/35 µg/day
Clinical Site (Study No. ESTN/2018/1607)	Synchron Research Services Pvt. Ltd.	Veeda Clinical Research Pvt. Ltd.	
Clinical Site Address	<u>Screening facility:</u> 1 st and 2 nd Floor, Swagat Plaza II, Iscon- Bopal Road, Ambli, Ahmedabad-380 056, Gujarat, India <u>Clinical Study Facility:</u> Clinical Department, 201 & 301, 2 nd & 3 rd Floor, Satva, Opp Bhavin School, Thaltej, Ahmedabad 380059, Gujarat, INDIA	Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India	
Analytical Site	(b) (4)		

Analytical Site Address	(b) (4)		
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete		<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☐ Pending For Cause Inspection ☒ Complete
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☐ Not granted ☒ N/A		
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate		
Formulation	☒ Adequate ☐ Inadequate ☐ Pending		
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A		
Deficiency Classification	☐ Major ☒ Minor (DRL) ☐ N/A		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date ¹ : May 2009/ Jul 2009, Oct 2016, Oct 2018, Nov 2019 RLD Number: 021180 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1	Fasting	150/35 µg/day	☐ Adequate ☒ Inadequate

¹ https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

1 EXECUTIVE SUMMARY

This application contains the results of a pivotal bioequivalence (BE) study with pharmacokinetic (PK) endpoints comparing a test product, Amneal Pharmaceuticals LLC's Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day to the corresponding reference standard, Xulane® (norelgestromin and ethinyl estradiol) 150 µg /35 µg/day Transdermal System (Mylan Technologies, Inc., ANDA 200910). The BE study was designed as a single-dose, **two-group**, two-way crossover study in healthy non-pregnant, non-lactating female subjects.

Since the subjects in the study were dosed in 2 groups, the data was analyzed by the assessor using SAS program with 'group-by-treatment (TRT*GRP) term' in the GLM model. The TRT*GRP interaction term was tested for statistical significance at (p< 0.1). The group-by-treatment interaction was found to be statistically insignificant for both Ethinyl Estradiol [AUCt (p=0.8927), AUCi (p=0.9216) and Cmax (p=0.6134)] and Norelgestromin [AUCt (p=0.7107), AUCi (p=0.7181) and Cmax (p=0.8743)]. The TRT*GRP interaction term was removed from the model for the final statistical analysis as per the current Division of Bioequivalence practice. The results are summarized in the tables below.

Ethinyl Estradiol (EE)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1 x 150 µg /35 µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N*	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	6381.51	72	6750.18	72	0.95	90.33	98.95
AUC _∞ (hr *pg/ml)	6459.66	72	6845.92	70**	0.94	90.05	98.87
Cmax (pg/ml)	46.96	72	46.76	72	1.00	95.91	105.16

* Seven subjects (Nos. (b) (6)) had at least one pre-dose concentration of ethinyl estradiol greater than 5% of their respective C_{max} and were excluded from the PK and statistical analysis.

**Subjec (b) (6) were excluded from AUC_i calculation with reference product treatment due to missing the last three and two time-points, respectively and unreliable estimation of elimination rate constant.

Norelgestromin (NGMN)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1x 150 µg /35µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	162429.8	78	160920.3	78	1.01	96.90	105.15
AUC _∞ (hr *pg/ml)	173116.7	78	171855.5	76**	1.01	96.65	104.99
Cmax (pg/ml)	1029.97	78	1027.76	78	1.00	96.03	104.58

*Subject (b) (6) had pre-dose concentration of norelgestromin greater than 5% of C_{max} with reference product treatment and was excluded from the PK and statistical analysis.

**Subject (b) (6) were excluded from AUC_i calculation due to missing the last three and two time-points with reference product treatment, respectively and unreliable determination of elimination phase.

The 90% confidence intervals (CIs) for the least square geometric mean ratios of AUC_{0-t} , $AUC_{0-\infty}$ and C_{max} for both Ethinyl Estradiol and Norelgestromin meet the acceptance criteria of 80.00-125.00%. However, the application was **inadequate** due to deficiencies related to bioanalytical method, observed pre-dose concentrations greater than 5% C_{max} for EE and NGMN at period I in some subjects and concerns on low loading dose of EE in the test formulation. The test formulation contains 0.289 mg loading dose of EE, which is only 54.5% of the amount in the RS (0.53 mg loading dose). In the pivotal BE study No. ESTN/2018/1607), the test and reference products were applied in the abdomen site. From the mean concentration-time profiles, it is noticed that concentrations of EE dropped significantly in test product from 72 to 168 hours compared to Xulane®. Based on discussion with the Office of Research Standards (ORS)², it raises concerns that the slower release observed in the test product may be due to the low loading dose of EE which might result in insufficient excess of drug available within the TDS after 72 hours to maintain the concentration gradient and driving force to sustain the same rate and extent of drug delivery as the reference TDS. The firm is asked to address this issue. In addition, the firm is asked to provide justification that the loading amount of EE is sufficient for other non-abdominal application sites (i.e., buttock, arm, and torso), where the absorption of NGMN and EE is approximately (b) (4) than the abdomen site.

Prior to conducting the passed current pivotal BE study, the firm conducted a pilot fasting study³ (16-VIN-0235, 34 subjects completed for NGMN and 33 subjects completed for EE) and a pivotal fasting study (16-VIN-0236, 59 subjects completed) with **different** test formulations. The 90% CIs for $L_n AUC_t$, AUC_i and C_{max} met the BE criteria for NGMN, however, the upper bounds of 90% CIs for all PK parameters are higher than 125.00% for EE in both studies. The firm applied the transdermal patches at abdominal site in both studies (b) (4)

(b) (4) Please see details at section 4.1.1.4.5. Due to the issue on loading amount of EE in the test formulation in the current pivotal study (No. ESTN/2018/1607), the firm will be asked to provide the full study reports of the failed pilot and pivotal studies for Agency's further evaluation, and provide composition of test formulations used in these studies, including the quantity in mg/patch for each active and inactive ingredient.

The applicant conducted its dissolution testing using FDA dissolution method [USP Apparatus V (Modified USP Type V (Paddle-over-disk)) at 50 rpm in 900 mL 0.1% Hydroxypropyl-beta-cyclodextrin at 32° C]. The dissolution data will be reviewed

² <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>, Document: A213950N000DB-MeetingMinutes01-04082020.docx

³ The firm claimed the fasting study No. 16-VIN-0235 as a pilot study. However, it is considered as a pivotal fasting study based on the subject numbers completed the study.

separately by the Division of Biopharmaceutics at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ) for establishing the batch releasing specifications and is inadequate per preliminary assessment pending the acceptance of FDA recommended dissolution acceptance criteria for the drug product.⁴ There is no waiver request submitted in the current application.

The applicant also submitted Adhesion study (ESTN/2018/1607) and skin Sensitization/Irritation study (No. GCPAMN002) in the current submission. The Division of Clinical Review will review the Adhesion and Sensitization/Irritation Studies.

Office of Study Integrity and Surveillance (OSIS) Inspections

Per GDRP, OSIS determines that inspections are not warranted at this time for both clinical^{5,6} and analytical⁷ sites as the outcome of previous inspections was 'No Action Indicated (NAI)'. In addition, the studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is complete.

In addition, since the PK endpoint study was conducted at Synchron clinical site, the assessor also conducted further analysis using DABERS tool. Based on DABERS finding, the possible data integrity was not identified at this stage.

The application is **inadequate** with the deficiencies mentioned above.

⁴ GDRP, ANDA-213950-ORIG-1, Biopharmaceutics Quality Review, (<https://panorama.fda.gov/task/view?ID=5dfb98460002425b1aabbba6d6ace592>)

⁵ GDRP, ANDA-213950-ORIG-1, Clinical PK/PD Sites, Site: SYNCHRON RESEARCH SERVICES PVT LTD, Decline to Inspect_A213950_Synchron_Research_Clin.Pdf, archived on 1/14/19 (<https://panorama.fda.gov/task/view?ID=5dfd477e005813c17105d93835539524>)

⁶ <https://panorama.fda.gov/task/view?ID=5cacbb2c00202fc0b73bc48ae547a7a9>

(b) (4)

2 TABLE OF CONTENTS

1	Executive Summary	3
2	Table of Contents	6
3	Submission Summary.....	7
3.1	Drug Product Information	7
3.2	PK/PD Information	7
3.3	OGD Recommendations for Drug Product	9
3.4	Pre-Study Bioanalytical Method Validation	11
3.5	In Vivo Studies.....	17
4	Appendix	26
4.1	Individual Study Reviews	26
4.1.1	Single-dose Fasting Bioequivalence Study.....	26
4.1.1.1	Study Design.....	26
4.1.1.2	Clinical Results.....	30
4.1.1.3	Bioanalytical Results	35
4.1.1.4	Pharmacokinetic Results.....	42
4.1.2	Single-Dose Failed Pivotal Fasting Bioequivalence Study.....	68
4.1.2.1	Study Design.....	68
4.1.2.2	Clinical Results.....	70
4.1.2.3	Bioanalytical Results	73
4.1.2.4	Formulation Data.....	78
4.1.2.5	Pharmacokinetic Results.....	78
4.1.3	Single-dose Failed Fasting Bioequivalence Study.....	81
4.1.3.1	Study Design.....	81
4.1.3.2	Clinical Results.....	82
4.1.3.3	Bioanalytical Results	85
4.1.3.4	Formulation Data.....	91
4.1.3.5	Pharmacokinetic Results.....	91
4.2	Formulation Data	94
4.2.1	Test Formulation.....	94
4.2.2	RLD formulation(NOT TO BE RELEASED UNDER FOIA)	97
4.2.3	RS formulation (NOT TO BE RELEASED UNDER FOIA)	98
4.2.4	Inactive Ingredients (IIG Table)	98
4.3	Dissolution Testing	104
	Dissolution Data	104
	Dissolution Profiles	111
	F2 Metric	112
4.4	Attachments	112
4.4.1	ANDA 213950 Phoenix project file	112
4.4.2	ANDA 213950 DABERS files	112
4.4.3	SAS Output.....	113
4.4.4	Outcome Page.....	116

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day
Reference Standard (RS) and Strength(s)	Xulane® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day
RS Holder; ANDA Number; Approval Date⁸	Mylan Technologies, Inc.; ANDA 200910; Approved on 04/16/2014
Reference Listed Drug (RLD) and Strength(s)	Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day
RLD Holder; NDA Number; Approval Date⁹	Janssen Pharmaceuticals, Inc.; NDA 021180; Approved on 11/20/2001; Discontinued (**Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**) ¹⁰

3.2 PK/PD Information¹¹

Most recent RLD label	 RS Xulane Label 04192017.pdf NG/G/J tube study: N/A
Indication	Xulane is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch. Limitation of Use: Xulane may be less effective in preventing pregnancy in women at or above 198 lbs (90 kg).

⁸ Per Orange Book,

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=200910#29696

⁹ Per Orange Book,

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021180#3757

¹⁰ <http://sharepoint.fda.gov/orgs/CDER->

[OGD/OGDP/DLRS/Lists/DLRS%20QuickNews/Attachments/26/2015-24622_PONDIMIN%20and%20Ponderex%20WERE%20WD%20for%20reasons%20of%20SE.pdf](http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/Lists/DLRS%20QuickNews/Attachments/26/2015-24622_PONDIMIN%20and%20Ponderex%20WERE%20WD%20for%20reasons%20of%20SE.pdf)

¹¹ <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f7848550-086a-43d8-8ae5-047f4b9e4382;>

Updated: April 19, 2017.

Boxed warning	WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, AND PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL Cigarette Smoking and Serious Cardiovascular Risks Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including Xulane, should not be used by women who are over 35 years of age and smoke. Risk of Venous Thromboembolism The risk of venous thromboembolism (VTE) among women aged 15 to 44 who used the norelgestromin and ethinyl estradiol transdermal system compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of norelgestromin and ethinyl estradiol transdermal system [see <i>Warnings and Precautions (5.1)</i>]. Pharmacokinetic (PK) Profile of Ethinyl Estradiol (EE) The PK profile for the norelgestromin and ethinyl estradiol transdermal system is different from the PK profile for oral contraceptives in that it has a higher steady state concentrations and a lower peak concentration. Area under the time-concentration curve (AUC) and average concentration at steady state (C_{ss}) for EE are approximately 60% higher in women using norelgestromin and ethinyl estradiol transdermal system compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, the peak concentration (C_{max}) for EE is approximately 25% lower in women using norelgestromin and ethinyl estradiol transdermal system. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using norelgestromin and ethinyl estradiol transdermal system compared with women using oral contraceptives containing 30 mcg to 35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including VTE [see <i>Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)</i>].
Bioavailability	The systemic delivery rate of NGMN and EE from norelgestromin and ethinyl estradiol transdermal system is approximately 150 mcg of NGMN and 35 mcg of EE per day based on a comparative analysis with intravenous (IV) data. Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours. Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application. In one of the clinical studies, concentrations across all subjects ranged from 0.305 to 1.53 ng/mL for NGMN and from 23 to 137 pg/mL for EE. Absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be <u>therapeutically equivalent</u>.
Food Effect	N/A
Tmax	Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours.
Metabolism	Since norelgestromin (NGMN) and ethinyl estradiol (EE) transdermal system is applied transdermally, first-pass metabolism (via the gastrointestinal tract and/or liver) of NGMN and EE that would be expected with oral administration does not occur. Hepatic metabolism of NGMN occurs and metabolites include norgestrel, which is highly bound to SHBG, and various hydroxylated and conjugated metabolites. EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.
Excretion	The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

Half-life	The elimination kinetics of NGMN and EE were consistent for all studies with half-life values of approximately 28 hours and 17 hours, respectively.
Dosage and Administration	The Xulane transdermal system uses a 28-day (4-week) cycle. A new patch is applied each week for 3 weeks (21 total days). Week 4 is patch-free. Withdrawal bleeding is expected during this time. Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time. Do not cut, damage or alter the Xulane patch in any way. If the Xulane patch is cut, damaged or altered in size, contraceptive efficacy may be impaired. On the day after Week 4 ends, a new 4-week cycle is started by applying a new patch. Under no circumstances should there be more than a 7-day patch-free interval between dosing cycles.
Maximum Daily Dose	1 patch /week (Norelgestromin: 150 µg and Ethinyl Estradiol: 35 µg)

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance¹²	 PSG NGMN EE TDS Jul 2019.pdf	
Summary of OGD or DB History	Approved ANDAs:	Yes, ANDA 200910 (RS)
	Pending ANDAs:	Yes, ANDA 213977 (Teva); ANDA 213950 (Amneal, current application)
	Controls: ¹³	Per GDRP, numerous controls are available for this drug product. There are 5 controls from Amneal and they are listed below.
	Protocols: ¹⁴	There are two protocols listed in the OGD database for Norelgestromin and Ethinyl Estradiol Transdermal Film Extended Release. Protocol # (03042) from (b) (4) and Protocol # (04049) from (b) (4).

¹² PSG: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

¹³ <https://panorama.fda.gov/search?objCode=ALL&allowRedirect=false&query=norelgestromin&showResultsPage=false#?facets=%5B%7B%22fieldName%22:%22categoryID%22,%22filters%22:%5B%22categoryID%22:%537669e800073f720fcf8b8f349f8fd9%22%5D%7D%5D>

¹⁴ <http://ogd.fda.gov/seltrack/Protocols.asp>, Search: Norelgestromin

	Pending Citizen Petitions and other legal and regulatory issues: ¹⁵ If yes, please comment.	☐ Yes ☒ No

Anneal submitted the following five Control Correspondences (CCs) for Norelgestromin and Ethinyl Estradiol Transdermal System:

1. Anneal contacted the Agency with CC No.15728669¹⁶, dated June 16, 2017 regarding IIG evaluation of Polyisobutylene/Polybutene Adhesive (b) (4) (b) (4) at (b) (4) and Polybutene (b) (4) (b) (4) at (b) (4), for which the Office of Generic Drugs (OGD) communicated that these inactive ingredients are below the same inactive ingredients in previously FDA approved drug products.
2. In CC No. 16990170,¹⁷ dated 08/14/2017, Anneal requested for the evaluation of Polyisobutylene/Polybutene Adhesive (b) (4). The OGD communicated that the amount of (b) (4) below the same inactive ingredient in previously FDA approved drug products. In the above CC also, Anneal requested for evaluation of (b) (4) (b) (4). Please refer to Section 4.2 for formulation details.
3. In CC No. 10376677,¹⁸ dated 09/26/2016, the applicant requested Agency's confirmation to use Xulane® as the reference standard (RS) for their generic drug development when conducting in vivo bioequivalence studies comparing a generic version of Ethinyl Estradiol and Norelgestromin Transdermal System, 0.035/0.15 mg per 24 hr. RLD Ortho Evra® was discontinued and the guidance was not updated at that time. On 10/12/2016, the Agency responded with the communication that the RLD link for ethinyl estradiol; norelgestromin transdermal extended release film BE guidance has been updated on the Product-Specific Recommendations for Generic Drugs website.
4. On 12/17/2018, Anneal submitted a CC (No. 27999717),¹⁹ requesting a clarification about an inclusion criterion recommended for all studies supporting a demonstration of BE in the PSG for Ethinyl Estradiol; Norelgestromin Extended-release (ER) Transdermal Delivery System (TDS), Recommended May 2009, Revised Jul 2009, Oct 2016, Oct 2018 that states “subjects with an intact uterus who have a baseline vaginal ultrasonography demonstrating inactive endometrial

¹⁵ DLRS policy updates as of 04/13/2020 in the link <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx>

¹⁶ <https://panorama.fda.gov/task/view?ID=5947d1d900b562ae14cf6f8131bf06b4>

¹⁷ <https://panorama.fda.gov/task/view?ID=599455be00605c7b4f24b17aff2ad069>

¹⁸ <https://panorama.fda.gov/project/view?ID=57e9786d0010871c40723e1a4499de78>

¹⁹ <https://panorama.fda.gov/task/view?ID=5c18231a001ebbd76515986fc75f539d>

lining with endometrial thickness less than 4 mm”. The Agency acknowledged Amneal’s concern that not all subjects would be comfortable with the approach, and that the criterion would lead to unpredictable enrollment and communicated that the Agency concurs that this inclusion criterion may be disregarded when conducting studies (with healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception) that support a demonstration of bioequivalence between test and reference Ethinyl Estradiol/Norelgestromin TDS, 0.035mg/24hr;0.15mg/24h.

- On 03/22/2018, Amneal contacted the Agency with CC No. 21822019²⁰ and submitted a statistical analysis plan (SAP), describing the planned analysis in detail as per the provisions in the PSG for its adhesion study (Protocol # 16-VIN-0236) conducted for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg/day. There is no communication from the Agency to the firm per GDRP. Per the current submission, this study (#16-VIN-0236) is a failed pivotal fasting study, for which the firm submitted all BE tables. Please refer to Section 4.1.2. for details.

3.4 Pre-Study Bioanalytical Method Validation

Ethinyl Estradiol

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4; refer 5314-bioanal-methval.pdf; Page No. 11 to 555 of 974
Analyte	Ethinyl estradiol
Internal standard (IS)	Ethinyl estradiol-d ₄
Method description	This method involves the extraction of Ethinyl estradiol and the internal standard Ethinyl estradiol-d ₄ from Human EDTA K ₂ Plasma <u>using a liquid-liquid extraction and derivatization procedure and LC-MS/MS determination</u> according to method SOP (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.600 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	1.00 Original validation report
Average recovery of drug (%CV)	QC1: 103.53% (3.89) QC2: 99.69% (6.34) QC3: 98.31% (3.26) Original validation report
Average recovery of IS (%CV)	109.73% (3.18) Original validation report
Standard curve concentrations (pg/mL)	1.00, 2.00, 4.00, 20.00, 40.00, 80.00, 160.00, 200.00 Partial validation 1
QC concentrations (pg/mL)	LLQC: 1.00, QC1: 3.00, QC2: 100.00, QC3: 150.00

²⁰ <https://panorama.fda.gov/project/view?ID=5ab8fa880087b5096b67e3063057eb36>

Information Requested	Data
	Partial validation 1
QC Intraday precision range (%)	0.87 to 6.03 Partial validation 1
QC Intraday accuracy range (%bias)	-7.17 to -3.07 Partial validation 1
QC Interday precision range (%)	1.54 to 9.84 Original validation report
QC Interday accuracy range (%bias)	1.85 to 8.90 Original validation report
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24h10min at room temperature Original validation report
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte : 325 days at -20°C Internal standard: 367 days at -20°C Original validation report
Processed stability (hrs) (equivalent to post-preparative stability)	71h50min at 4°C Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20°C (fortified with 17-Desacetylnorgestimate) Interference report
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	105 days at -20°C (fortified with 17-Desacetylnorgestimate) Interference report (Revision 02)
Dilution integrity	DQC diluted 1/20: 2000.00 pg/mL %CV: 0.59 %Bias: 1.41 Original validation report
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard Original validation report

Norelgestromin

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4; refer 5314-bioanal-methval.pdf; Page No. 556 to 974 of 974
Analyte	17-desacetylnorgestimate
Internal standard (IS)	17-desacetylnorgestimate-d ₆
Method description	This method involves the extraction of 17-desacetylnorgestimate and the internal standard 17-desacetylnorgestimate-d ₆ from Human EDTA K ₂ Plasma using an automated liquid-liquid extraction with methyl tert-butyl ether procedure and LC-MS/MS determination

Information Requested	Data
	according to method SOP (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.200 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	50.00 Original validation report
Average recovery of drug (%CV)	QC1: 95.13 (1.13) QC2: 93.55 (1.69) QC3: 91.59 (2.23) Original validation report
Average recovery of IS (%CV)	103.42 (2.27) Original validation report
Standard curve concentrations (pg/mL)	50.00, 100.00, 200.00, 300.00, 600.00, 1800.00, 2400.00, 3000.00 Original validation report
QC concentrations (pg/mL)	LLQC: 50.00, QC1: 150.00, QC2: 1500.00, QC3: 2250.00 Original validation report
QC Intraday precision range (%)	1.00 to 4.95 Original validation report
QC Intraday accuracy range (%bias)	-6.05 to 0.77 Original validation report
QC Interday precision range (%)	4.58 to 5.64 Original validation report
QC Interday accuracy range (%bias)	-3.39 to 3.32 Original validation report
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24h00min at room temperature Original validation report
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte : 254 days at -20°C Internal standard: 159 days at -20°C Original validation report
Processed stability (hrs) (equivalent to post-preparative stability)	95h52min at room temperature Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20 °C (fortified with Ethinyl estradiol) Interference report
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	909 days at -20°C (fortified with Ethinyl Estradiol) Interference report (Revision 03)
Dilution integrity	DQC diluted 1/20: 30000.00 pg/mL %CV: 1.56 %Bias: -4.85 Original validation report

Information Requested	Data
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard. Original validation report

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	☒ Yes ☐ No
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☐ Yes ☒ No

Comments on the Pre-Study Method Validation: Inadequate

Ethinyl Estradiol (EE):

- EE was measured by LC-MS/MS after liquid-liquid extraction from human plasma and derivatization. Ethinyl Estradiol-d₄ used as internal standard. The firm did not mention what type of derivatization procedure was used after extraction. The firm will be asked to provide the detailed analytical procedure for liquid-liquid extraction and derivatization.
- The firm used di-potassium ethylenediaminetetraacetic acid (K₂EDTA) as anticoagulant in its pre-study method and validation and in the BE study (No. ESTN/2018/1607) samples. The calibration standards and quality control samples were prepared with human plasma containing K₂EDTA.
- Per the method validation report, the firm conducted 2 partial validations.
 1. Project Number: 185125ATBK: The method was modified to truncate the analytical range from 1-400 pg/mL to 1-200 pg/mL.
 2. Project Number: 185108 (b) (4): The method was to truncate the analytical range from 1-400 pg/mL to 1-100 pg/mL.

In the current application, the firm used analytical range of 1-200 pg/mL, which was validated in the partial validation 1.

- The firm evaluated the potential interference by 17-desacetylnorgestimate with the ethinyl estradiol assay in the validation. The firm conducted specificity study fortified with NGMN to demonstrate no effect on the quantitation of EE and its IS. One blank and one zero standard samples were fortified with 17-

desacetylnorgestimate at 2970 pg/mL (approximately expected maximal matrix concentrations). Fortified samples were processed and analyzed in triplicate. The results met the pre-established acceptance criteria.

- The long term storage data of ethinyl estradiol for 105 days at -20°C (fortified with 17-Desacetylnorgestimate at 2970 pg/mL) exceed the storage period of the pivotal BE study (No. ESTN/2018/1607) samples for 102 days.
- One subject received tranexamic acid and one subject (b) (6) received diclofenac diethylamine, salicylate methyl, menthol and benzyl alcohol during the clinical portion of the study. A specificity test was performed in order to determine if the presence of tranexamic acid, diclofenac diethylamine, salicylate methyl, menthol and benzyl alcohol could potentially affect the quantification of ethinyl estradiol. Based on the interference evaluation data, it is confirmed that no significant effect is observed in the presence of these concomitant medications on the quantification of ethinyl estradiol for the pivotal study ((No. ESTN/2018/1607). In addition, the firm conducted the interference for EE analysis in the presence of common concomitant drugs, acetaminophen, acetylsalicylic acid, caffeine, cotinine, dextromethorphan, dimenhydrinate, diphenhydramine, ibuprofen, levonorgestrel, nicotine, pseudoephedrine and salicylic acid and the results met the pre-established acceptance criteria.

Norelgestromin (NGMN):

- Per the bioanalytical method validation report, the firm analyzed 17-desacetylnorgestimate. Per PubChem,²¹ Norelgestromin is synonymous to 17-desacetylnorgestimate with molecular formula of C₂₁H₂₉NO₂ and molecular weight of 327.5 g/mol. The firm also mentioned the same molecular formula and molecular weight in drug substance nomenclature for NGMN.²²
- 17-desacetylnorgestimate-d₆ was used as internal standard. The firm used K2EDTA as anticoagulant in method validation, BE study sample analysis and in the calibration standards and quality control samples. NGMN was measured by LC-MS/MS after liquid-liquid extraction with methyl tert-butyl ether procedure. However, the firm did not provide detailed procedure for the extraction method. The firm will be asked to provide this information.
- Per the method validation report, the firm conducted 2 revisions of original method validation
 1. Project Number: 185125ATBK: The validation report was revised to be compliant with current regulations and to add stability data in matrix at -80°C (29 days).

²¹ <https://pubchem.ncbi.nlm.nih.gov/compound/Norelgestromin#section=Wikipedia>

²² <\\cdsesub1\evsprod\anda213950\0001\m3\32-body-data\32s-drug-sub\norelgestromin-usp-gedeon-richter\32s1-gen-info\32s11-nomenclature.pdf>

2. Project Number: 195007AUOL: The validation report was revised to evaluate the Specificity with 17-Desacetylnorgestimate supersede the potentially interfering concomitant medication and metabolite effect and perform Long-term stability of analyte in matrix at -20°C and -80°C (105 days) (extended).
- The firm conducted specificity study fortified with EE to demonstrate no effect on the quantitation of NGMN and its IS in the presence of EE. One blank and one zero standard samples were fortified with ethinyl estradiol at ~198 pg/mL (approximately expected maximal matrix concentrations). Fortified samples were processed and analyzed in triplicate. The results met the pre-established acceptance criteria.
 - The long term storage data of NGMN for 909 days at -20°C (fortified with Ethinyl Estradiol at 198 pg/mL) exceed the storage period of the pivotal BE study (No. ESTN/2018/1607) samples for 100 days.
 - Low QC (QC1 – 150 pg/ml) samples were fortified with the following drugs at their respective therapeutic concentrations: acetaminophen, acetylsalicylic acid, caffeine, cotinine, dextromethorphan, dimenhydrinate, diphenhydramine, ethinyl estradiol, ibuprofen, levonorgestrel, nicotine, pseudoephedrine and salicylic acid. These fortified quality control samples were processed, analyzed, and their concentrations and biases were calculated to evaluate the potential interference of each drug with the 17-desacetylnorgestimate assay. The results met the pre-established acceptance criteria. In addition, the drugs administered in the BE study, tranexamic acid, diclofenac diethylamine, salicylate methyl, menthol and benzyl alcohol during the clinical portion of the study did not interfere with the analysis of NGMN.

The pre-study validation data of ethinyl estradiol and norelgestromin is **inadequate**.

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)***						Study Report Location
					C _{max} (pg/mL)	*T _{max} (h)	AUC _(0-t) (pg.h/mL)	AUC _(0-∞) (pg.h/mL)	t _½ (h)	K _{el} (1/h)	
Norelgestromin											
ESTN/2018/1607	A Pivotal, Open Label, Balanced, Randomised, Two-Treatment, Two-Sequence, Two-Period, Single Application, Two-Way Crossover, Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals LLC with Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System 150 mcg/35 mcg per day manufactured for Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A in Normal Healthy, Adult, Human, Female Subjects under Fasting Conditions.	A randomised, open label, balanced, two treatment, two period, two sequence, single application, crossover design	Test Product – T Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day Patch 150/35 mcg per day Patch Transdermal [Batch # PW-ST-18020A]	79** completing (#F) Healthy subjects 30.29 Years (22-34)	1086 ± 359 (33.1%)	84.00 (48.00 - 168.00)	170727 ± 54116 (31.7%)	180292 ± 56911 (31.6%)	33.9 ± 7.40 (21.8%)	0.0215 ± 0.0052 (24.3%)	Module 5.3.1.2
			Reference Product-R: Xulane® (norelgestromin and Ethinyl estradiol transdermal system) 150/35 mcg per day		1087 ± 346 (31.8%)	84.00 (60.00 - 168.03)	171310 ± 52952 (30.9%)	180911 ± 55505 (30.7%)	33.0 ± 7.52 (22.8%)	0.0220 ± 0.0049 (22.2%)	

			Patch 150/35 mcg per day Patch Transdermal [Lot # 3098718]								
*For T_{max} median (min – max) ** Subjects who completed the bioequivalence study ***N=72 considering exclusion of subjects with pre-dose concentration more than 5% of C_{max}											

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)***						Study Report Location
					C _{max} (pg/mL)	*T _{max} (h)	AUC _(0-t) (pg.h/mL)	AUC _(0-∞) (pg.h/mL)	t _½ (h)	K _{el} (1/h)	
Ethinyl Estradiol											
ESTN/2018/1607	A Pivotal, Open Label, Balanced, Randomised, Two-Treatment, Two-Sequence, Two-Period, Single Application, Two-Way Crossover, Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals LLC with Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System 150 mcg/35 mcg per day manufactured for Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A in Normal Healthy, Adult, Human, Female Subjects under Fasting Conditions.	A randomised, open label, balanced, two treatment, two period, two sequence, single application, crossover design.	Test Product – T Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day Patch 150/35 mcg per day Patch Transdermal [Batch # PW-ST-18020A] Reference Product-R: Xulane® (norelgestromin and Ethinyl estradiol transdermal system) 150/35 mcg per day Patch 150/35 mcg per day Patch Transdermal	79** completing (#F) Healthy subjects 30.29 Years (22-34)	49.6 ± 16.7 (33.6%)	60.00 (36.00) - 144.00	6724 ± 2140 (31.8%)	6789 ± 2150 (31.7%)	18.6 ± 3.59 (19.3%)	0.0386 ± 0.0074 (19.2%)	Module 5.3.1.2
					50.1 ± 18.4 (36.7%)	84.00 (36.00) - 168.05	7334 ± 2796 (38.1%)	7434 ± 2840 (38.2%)	18.3 ± 3.73 (20.4%)	0.0393 ± 0.0076 (19.4%)	

[Lot # 3098718]

*For T_{max} median (min – max)

** Subjects who completed the bioequivalence study

***N=78 considering exclusion of subjects with pre-dose concentration more than 5% of C_{max}**Pivotal Fasting Study (No. 16-VIN-0236) - FAILED**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg*h/mL)	AUC _∞ (pg*h/mL)	T _{1/2} (hr)	K _{el} (hr ⁻¹)	
Ethinyl Estradiol											
16-VIN-0236	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl estradiol Transdermal System, 150/35	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-application, crossover bioequivalence with pharmacokinetic endpoints and adhesion study in healthy, adult, human female subjects under fasting conditions.	Test Product (T) Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day, 1 x 150/35 mcg, (Transdermal) Patch applied on abdomen, Batch No.: PW-ST-17042A	Completed : 59 ** healthy, adult, human female subjects Age: 29.51 ± 3.67 (21.00 – 34.00 yrs)	59.7 ± 20.9 (35.1%)	60.00 (36.00 - 168.00)	8418 ± 2875 (34.2%)	8514 ± 2920 (34.3%)	19.4 ± 3.54 (18.3%)	0.0370 ± 0.0071 (19.2%)	Not Applicable
			Reference Product (R) Xulane® (norelgestromin and ethinyl		50.3 ± 19.6 (39.0%)	84.00 (36.00 -)	7234 ± 3036 (42.0%)	7344 ± 3117 (42.4%)	19.2 ± 4.01 (20.8%)	0.0376 ± 0.0080	

mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting conditions.		estradiol transdermal system) 150/35 mcg per day, 1 x 150/35 mcg, (Transdermal) Patch applied on abdomen, Lot No.: 3086481			168.00)				(21.2%)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUC _{0-t} (pg*h/mL)	AUC _∞ (pg*h/mL)	T1/2 (hr)	Kel (hr ⁻¹)	
Norelgestromin											
16-VIN-0236	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-application, crossover bioequivalence with pharmacokinetic endpoints and adhesion study in healthy, adult, human female subjects under fasting conditions.	Test Product (T) Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day, 1 x 150/35 mcg, (Transdermal) Patch applied on abdomen, Batch No.: PW-ST-17042A	Completed : 59 healthy, adult, human female subjects Age: 29.51 ± 3.67 (21.00 – 34.00 yrs)	1284 ± 390 (30.3%)	84.00 (60.00 - 144.02)	203240 ± 59448 (29.3%)	215929 ± 62709 (29.0%)	35.2 ± 7.92 (22.5%)	0.0207 ± 0.0049 (23.4%)	Not Applicable
			Reference Product (R) Xulane® (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day, 1 x 150/35 mcg,		1127 ± 333 (29.5%)	96.00 (48.00 - 168.00)	177981 ± 50855 (28.6%)	189322 ± 54237 (28.6%)	34.7 ± 8.90 (25.6%)	0.0213 ± 0.0056 (26.2%)	

estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting conditions.	(Transdermal) Patch applied on abdomen, Lot No.: 3086481										
**Fifty-eight (58) subjects were used in the comparisons of K_{el} , $T_{1/2}$, and AUC_{∞} .											

Pivotal Fasting Study (No. 16-VIN-0235)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Arithmetic Mean Parameters (+/-SD) (%CV) (N = 34)							Study Report Location
					C _{max} (pg/mL)	#T _{max} (hr)	AUC _{0-t} (hr* pg/mL)	AUC _{0-∞} (hr* pg/mL)	t _{1/2} (hr)	K _{el} (1/hr)	AUC _{%Extra p obs} (%)	
Norelgestromin												
16-VIN-0235	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence	Test Product (T) Norelgestromin and Ethinyl Estradiol transdermal System 150/35 mcg per day, Administered 'Transdermal', (Batch No. B10103-072)	Completed: 34 healthy, adult, human Female subjects Mean Age 30.26 years (Range: 22 to 34 years)	1137.620 ± 354.4263 (31.16%)	84.000 (60.00 - 144.03)	171693.069 ± 53249.8628 (31.01%)	179609.872 ± 54843.4349 (30.53%)	32.648 ± 7.3966 (22.66%)	0.0223 ± 0.00491 (22.06%)	4.563 ± 2.5710 (56.34%)	Not Applicable

Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting condition	nce with Pharmacokinetic Endpoints and Adhesion Study in Healthy, Adult, Human Female Subjects under fasting condition.	Reference Product (R) Xulane™ (norelgestromin and Ethinyl estradiol transdermal system) 150/35 mcg per day, Administered 'Transdermal', (Lot No. 615264)		1134.693 ± 440.2067 (38.80%)	84.050 (60.00 - 168.02)	170817.930 ± 61499.0771 (36.00%)	178603.277 ± 62509.8553 (35.00%)	31.885 ± 6.7872 (21.29%)	0.0227 ± 0.00504 (22.18%)	4.656 ± 2.4977 (53.64%)	

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Arithmetic Mean Parameters (+/-SD) (%CV) (N = 34)							Study Report Location
					C _{max} (pg/mL)	#T _{max} (hr)	AUC _{0-t} (hr* pg/mL)	AUC _{0-∞} (hr* pg/mL) @	t _½ (hr) @	K _{el} (1/hr) @	AUC _{-%} Extrapolation (%) @	
Ethinyl Estradiol												
16-VIN-0235	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting condition	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study in Healthy, Adult, Human Female Subjects under fasting condition.	Test Product (T) Norelgestromin and Ethinyl Estradiol transdermal System 150/35 mcg per day, Administered 'Transdermal', (Batch No. B10103-072)	Completed: 34 healthy, adult, human Female subjects Mean Age 30.26 years (Range: 22 to 34 years)	63.636 ± 23.0142 (36.17%)	84.000 (36.00 - 144.03)	9038.836 ± 3349.9417 (37.06%)	9142.716 ± 3403.5482 (37.23%)	18.574 ± 3.7997 (20.46%)	0.0388 ± 0.00795 (20.47%)	1.069 ± 0.8885 (83.15%)	Not Applicable
			Reference Product (R) Xulane™ (norelgestromin and Ethinyl estradiol transdermal system) 150/35 mcg per day, Administered 'Transdermal', (Lot No. 615264)		51.136 ± 20.6592 (40.40%)	84.000 (36.00 - 120.10)	7232.828 ± 2921.9058 (40.40%)	7379.006 ± 2993.1146 (40.56%)	18.064 ± 3.9323 (21.77%)	0.0399 ± 0.00785 (19.65%)	1.071 ± 0.8804 (82.19%)	
# For T _{max} median (min – max), @N = 33 for Reference Product (R)												

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	ESTN/2018/1607			
Study Title	A Pivotal, Open Label, Balanced, Randomised, Two-Treatment, Two-Sequence, Two-Period, Single Application, Two-Way Crossover, Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals LLC with Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System 150 mcg/35 mcg per day manufactured for Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A in Normal Healthy, Adult, Human, Female Subjects under Fasting Conditions.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location Study Report Validation Report Bioanalytical Report	Module 5.3.1.2			
	Module 5.3.1.4			
	Module 5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax #)	<u>Screening facility:</u> Synchron Research Services Pvt. Ltd. 1st and 2nd Floor, Swagat Plaza II, Iscon- Bopal Road, Ambli, Ahmedabad- 380 056, Gujarat, India Telephone: +91- 2717 - 235282, 235283; Fax: +91-2717-230919 <u>Clinical Study Facility:</u> Synchron Research Services Pvt Ltd, Clinical Department, 201 & 301, 2nd & 3rd Floor, Satva, Opp Bhavin School, Thaltej, Ahmedabad 380059, Gujarat, INDIA Telephone: +91-79-26853415, 26854063, 40235397; Fax: +91-2717-230919			
Principal Clinical Investigator (Name, Email)	Dr. Digant Banerjee, M.B.B.S. digant@synchronresearch.com			
Dosing Dates	Group I Period I: 03/09/2019 Period II: 04/09/2019 Group II Period I: 03/26/2019 Period II: 04/25/2019			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Principal Analytical Investigator (Name, Email)	(b) (4)
Analysis Dates	
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	Ethinyl estradiol (190032AUTI): a) 102 days (09-MAR-2019 to 19-JUN-2019) b) -20°C 17-desacetylnorgestimate (190032AUTJ): a) 100 days (09-MAR-2019 to 17-JUN-2019) b) -20°C
Long-Term Storage Stability (LTSS) Coverage (no. days @ °C) temp	Ethinyl estradiol (190032AUTI): 105 days at -20°C (fortified with 17-Desacetylnorgestimate) 17-desacetylnorgestimate (190032AUTJ): 909 days at -20°C (fortified with Ethinyl Estradiol)
LTSS Data Location	Ethinyl estradiol (190032AUTI): Module 5.3.1.4; refer 190032-bioanalyt-methval.pdf; Analytical Method Validation Report No. 75066AKHL, Table 4.2A on Page. no. 462 of 974 17-desacetylnorgestimate (190032AUTJ): Module 5.3.1.4; refer 190032-bioanalyt-methval.pdf; Analytical Method Validation Report No. 145069AKFA, Table 5.3A on Page. no. 866 of 974

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day	Xulane® (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day
Manufacturer	Anneal Pharmaceuticals LLC	Mylan Pharmaceuticals Inc. Morgantown, WV26505 U.S.A. (Manufactured For)
Batch No./Lot No.	PW-ST-18020A	3098718
Manufacturing Date	10/02/2018	Not applicable
Expiration Date	Not applicable	04/2020
Strength	150/35 mcg per day	150/35 mcg per day
Dosage Form	Transdermal Patch	Transdermal Patch

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Bio-batch Size	(b) (4) eet	Not Applicable		
Production Batch Size	(b) (4) feet	Not Applicable		
Potency	Norelgestromin - 100.8 %	Norelgestromin - 101.9 %		
	Ethinyl Estradiol - 97.8 %	Ethinyl Estradiol - 99.2 %		
Content Uniformity (mean, %CV) - Ethinyl Estradiol	No. of units – 10	No. of units - 10		
	Min.	(b) (4)		
	Max	(b) (4)		
	Mean	98.6	Mean	99.2
	AV	1.6	AV	1.4
Content Uniformity (mean, %CV) - Norelgestromin	Min.	(b) (4)		
	Max	(b) (4)		
	Mean	101.0	Mean	102.0
	AV	2.2	AV	2.1
Dose Administered	150/35 mcg per day for 07 days	150/35 mcg per day for 07 days		
Route of Administration	Topical	Topical		

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☒ Yes ☐ No The Batch numbers of Reference product are different in BE study and Dissolution Study.
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☐ Yes ☐ No ☒ NA
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 84 Dosed: 84 in Period I; 81 in Period II Completed: 79 Samples Analyzed: 79 Statistically Analyzed: NGMN: 78; EE: 72
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2 (Group I: Subject Nos. (b) (6) Group II: Subject Nos. (b) (6))
Washout Period	21 days washout period after last blood withdrawal of first period during cohort I and 20 days washout period after last blood withdrawal of first period during cohort II
Randomization	☒ Yes ²³ ☐ No
Blood Sampling Times	Pre-patch application (collected within 01.00 hour prior to patch application) and at 02.00, 04.00, 06.00, 08.00, 12.00, 16.00, 20.00, 24.00, 30.00, 36.00, 48.00, 60.00, 72.00, 84.00, 96.00, 120.00, 144.00, 168.00, 192.00, 216.00 and 240.00 hours post application in each study period
IRB Approval	☒ Yes Date: 02/26/2019 ☐ No
Informed Consent	☒ Yes Date: 02/26/2019 ☐ No
Length of Fasting	at least 10.00 hours before patch application
Length of Confinement	subjects housed in the clinical facility at least 11.50 hours prior to patch application and remained in-house until 168.00 hours post-application in the study
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

Comments on Study Design: Adequate

- In accordance with the PSG, the BE study with PK endpoint study was designed as a single dose (application of 1 TDS of Ethinyl estradiol, Norelgestromin 150/35 µg), two-treatment, two-period crossover BE study in healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
- For all subjects, TDS was applied on subject's clean and dry area on **abdomen** by the trained personnel as per the randomization schedule in each study period at ambient temperature in semi recumbent position and worn for 7 days and blood sample collection was up to 240 hours (i.e., 10 days). Per RS label, the elimination

²³ <\\cdsesub1\evsprod\anda213950\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\estm-2018-1607-fast\random-drug-dispens-form.pdf>

half-life of NGMN and EE were approximately 28 hours and 17 hours, respectively. The sampling time up to 240 hours is sufficient to capture absorption, C_{max} and elimination phase, and the washout period of 20 to 21 days is sufficient for complete elimination of the analytes from the body (greater than 5 times of the elimination half-life).

- Adhesion scoring was done immediately after patch application (00.00 hours) and at 24.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00 (just prior to patch removal) hours post patch application. Adhesion assessment analyses were performed for eighty-three (83) subjects. The adhesive properties of Amneal's are non-inferior to those of RS, Xulane®.
- The applicant's BE study design complies with the recommendations in PSG and is adequate.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. ESTN/2018/1607			
		Treatment Groups	
		Test Product (T) N = 79	Reference Product (R) N = 79
Age (years)	Mean ± SD	30.29 ± 2.64	30.29 ± 2.64
	Range	22 – 34	22 - 34
Age Groups	< 18	-	-
	18 – 40	79(100.00 %)	79(100.00 %)
	41 – 64	-	-
	65 – 75	-	-
	> 75	-	-
Sex	Male	-	-
	Female	79(100.00 %)	79(100.00 %)
Race	Asian	79(100.00 %)	79(100.00 %)
	Black	-	-
	Caucasian	-	-
	Hispanic	-	-
	Other	-	-
BMI	Mean ± SD	26.07 ± 2.41	26.07 ± 2.41

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

(kg/m ²)	Range	19.23 - 29.79	19.23 - 29.79
Height (m)	Mean ± SD	1.53 ± 0.05	1.53 ± 0.05
	Range	1.43 - 1.68	1.43 - 1.68
Weight (kg)	Mean ± SD	61.41 ± 6.65	61.41 ± 6.65
	Range	51.70 - 78.10	51.70 - 78.10

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. ESTN/2018/1607				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject did not turn up for period II check-in activity.	II	NO	NA
	Subject voluntarily withdrew her consent from the study after 76.00 hours post patch application lunch during period II.	II	NO	NA
	Subject voluntarily withdrew her consent from the study after 84.00 hours post patch application activity during period II.	II	NO	NA
	Subject voluntarily withdrew her consent from the study after 04.00 hours post patch application lunch activity during period I.	I, II	NO	NA
	Subject did not turn up for period II check-in activity.	II	NO	NA

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No. –ESTN/2018/1607	
	Test	Reference
Reproductive system and breast disorders		
Vaginal haemorrhage	01 (1.22%)	-
Metrorrhagia	04 (4.88%)	02 (2.41%)

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Menorrhagia	-	03 (3.61%)
Musculoskeletal and connective tissue disorders		
Arthralgia	01 (1.22%)	-
Nervous system disorders		
Headache	-	02 (2.41%)
Skin and subcutaneous tissue disorders		
Dry skin*	-	01 (1.21%)
Total	06(7.32%)	08 (9.64%)

Note: Total 82 subjects were exposed with test product T and 83 subjects were exposed with reference product R.

*This AE was related to patch.

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
N/A	N/A	N/A	N/A	N/A	N/A

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A This is not an oral dosage form
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. ESTN/2018/1607		
Type	Subject #s (Test T)	Subject #s (Reference R)
Serum β -HCG test should be performed at the time of check-in. However, for few volunteers in period-I of cohort-II, serum β -HCG test was performed at the time of re-screening instead of check-in. For these subjects, date of re-screening and check-in date of period-I of	-	-

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Study No. ESTN/2018/1607		
Type	Subject #s (Test T)	Subject #s (Reference R)
cohort-II was same and blood sample for re-screening (on check-in day) was collected as per final protocol amendment 02 to final protocol version 02. Hence to prevent additional blood loss and to avoid housing deviation, serum β -HCG test was performed prior to initiation of check-in activity instead of after initiation of check-in activity.		(b) (6)
Adhesion score and Digital photography was to be performed within ± 10 minutes and ± 15 minutes of the scheduled time respectively. However, due to delay in blood sample collection in respective time point for few subjects and subjects reported late, adhesion scoring and digital photography was not performed within stipulated time as specified in protocol during both the cohorts.		
Patch should be removed at 168.00 hours after application within +5 minutes of schedule time. However, due to delay in blood sample collection and some procedural delay in activity for few subjects, patch was not removed within window period specified in protocol.		
In period I and II, there were few PK blood sampling time deviations occurred during the study, but these deviations were taken into account while PK calculations. For the subjects who did not turn up for 192.00, 216.00 and 240.00 hours post-dose ambulatory visit, their respective time point's vital signs were not taken.		
Clinical examination, vital sign measurement and clinical laboratory test were not performed at the end of the study for Subject (b) (6) and (b) (6) as they did not turn up for end of the study visit. Subject (b) (6) did not turn up for check-in period-II and Subject No. (b) (6) voluntarily withdrawn from the study in period-I. Subject (b) (6) and (b) (6) both were repeatedly contacted for end of study safety sample but they did not turn up for end of study visit.		
Subjects were asked about wellbeing status at the time of each vital sign measurement. However, study personnel missed to ask "Wellbeing" status to Subject (b) (6) 192.00 hrs post dose ambulatory visit in period-I and Subject (b) (6) during check-in vital in period-I.		

Study No. ESTN/2018/1607		
Type	Subject #s (Test T)	Subject #s (Reference R)
B.P., pulse rate and temperature should be monitored in sitting posture at 192.00 and 216.00 hours ($\pm$ 120 minutes) post patch application. However, for Subject (b) (6) at 192.00 hours post patch application ambulatory visit in period-II, vital sign was not recorded within $\pm$ 120 minutes of schedule time as subject reported late for the above mentioned ambulatory visit.		(b) (6)
Patch Site examination should be done at about 06.00, 12.00, 24.00, 36.00, 48.00, 60.00, 72.00, 84.00, 96.00, 120.00, 144.00 and 168.00 hours (just prior to patch removal) after application in each period. However, due to oversight, it was missed to examine the patch site of subject number (b) (6) at 84.00 hours post patch application in period-II.		

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Adequate

Dropouts

- Out of total 84 subjects enrolled in the fasting BE study, 5 subjects dropped out from the study. Two Subjects (Nos. (b) (6)) did not turn up for period II check-in. 3 Subjects (Nos. (b) (6)) withdrew their consents after the application of patches in Period II, Period II and Period I, respectively. 79 Subjects completed both periods of the study.

Adverse Events

- A total of fourteen (14) AEs were reported by fourteen (14) subjects during the study. Out of these, eight (08) AEs were reported after administration of Reference product and six (06) AEs were reported after administration of Test product. Out of fourteen (14) AEs, twelve (12) AEs had possible relationship with the Investigation Product (IP), one AE had unlikely relationship with the IP and one AE was unrelated to IP (it was related to patch). Out of fourteen (14) AEs, twelve (12) AEs were mild in nature while two (02) AEs were moderate in nature. All the fourteen (14) AEs were resolved.
- There were no deaths, serious or significant AEs during the conduct of the study.

Protocol Deviations

- In period I and II, there were few PK blood sampling time deviations occurred during the study, but the firm used actual time points in final PK calculations and these deviations are unlikely to have any impact the study outcome.
- Other deviations are related to deviations in Serum β -HCG screening, adhesion score and digital photography scheduled times, procedural delay in patch removal at 168 hrs, missing vital sign measurements for those who did not turn up for ambulatory sample collection, missing end of study clinical examination, especially for withdrawn subjects even after efforts to contact them, missing B.P., pulse rate and temperature measurements at ambulatory visit, missing patch site examination for one subject ((b) (6)) at 84 hrs in period II. The patch removal deviation was from 1-6 minutes beyond the scheduled time. The firm used actual time points for sample collection and these deviations will not likely affect the PK analysis results. All other deviations are minor and documented and are not likely to have impact on the outcome of the BE study.

Overall, the firm’s handling of dropouts, adverse reactions and protocol deviations are acceptable.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Sample Reassays and Reporting of Final Concentrations
		Codification and Reporting Process
		Chromatographic Acceptance Criteria and Verification of Chromatograms
		Determination of Bioanalytical Method Reproducibility Using Incurred Samples
		Bioanalytical Chromatographic Method Validation

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No.190032AUTI Ethinyl estradiol

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Parameter	Standard Curve Samples							
Concentration (pg/mL)	1.00	2.00	4.00	20.00	40.00	80.00	160.00	200.00
Interday Precision (%CV)	4.17	2.94	1.60	1.48	1.18	1.32	1.50	1.50
Interday Accuracy (%bias)	-4.00	2.00	9.50	5.05	-4.35	-4.44	0.64	-5.04
Linearity	0.9942 to 0.9969							
Linearity Range (pg/mL)	1.00 to 200.00							
Sensitivity/LOQ (pg/mL)	1.00							
Bioequivalence Study No.190032AUTI								
Ethinyl estradiol								
Parameter	Quality Control Samples							
Concentration (pg/mL)	3.00		10.00		100.00		150.00	
Interday Precision (%CV)	8.67		2.32		2.10		2.33	
Interday Accuracy (%bias)	0.00		-5.20		-5.57		-4.66	

Bioequivalence Study No.190032AUTJ								
17-desacetylnorgestimate								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	50.00	100.00	200.00	300.00	600.00	1800.00	2400.00	3000.00
Interday Precision (%CV)	3.47	3.20	3.00	2.80	2.61	2.87	2.48	3.16
Interday Accuracy (%bias)	-0.18	0.47	-0.27	-0.04	0.63	-0.13	0.15	-0.58
Linearity	0.9973 to 0.9996							
Linearity Range (pg/mL)	50.00 to 3000							
Sensitivity/LOQ (pg/mL)	50.00							
Bioequivalence Study No.190032AUTJ								
17-desacetylnorgestimate								
Parameter	Quality Control Samples							
Concentration (pg/mL)	150.00		250.00		1500.00		2250.00	
Interday Precision (%CV)	4.63		4.67		3.64		4.22	
Interday Accuracy (%bias)	-1.61		-2.79		-3.14		-2.42	

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly (Subjects 1 – 20)
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Ethinyl Estradiol

190032AUTI								
Module 5.3.1.4, 190032-bioanalyt-report.pdf, Table no. 3 on Page no. 66-67 & Table no. 4 on Page no. 68 of 4620								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	8	5	0.23	0.14	8	5	0.23	0.14
The internal standard response is lower than 5% of the mean internal standard responses	1	0	0.03	0.00	1	0	0.03	0.00
Sample reanalyzed to obtain confirming value	26	5	0.75	0.14	1	0	0.03	0.00
Total	35	10	1.01	0.29	10	5	0.29	0.14

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Norelgestromin

190032AUTJ								
Module 5.3.1.4, 190032-bioanalyt-report.pdf, Table no. 11 on Page no. 141 & Table 12 on Page no. 142 of 4620								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	2	1	0.06	0.03	2	1	0.06	0.03
Incomplete analysis	3	0	0.09	0	3	0	0.09	0.00
Sample reanalyzed to obtain confirming value	0	1	0	0.03	0	0	0.00	0.00
Total	5	2	0.14	0.06	5	1	0.14	0.03

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☐ N/A

Comments on Bioanalytical Results: Adequate

Ethinyl Estradiol (EE)

- Out of 46 Analytical Runs, 2 Runs (Run No. 34 including Subjects (b)(6) and Run No. 35 including Subjects (b)(6)) were rejected, both of them were due to less than 75% Calibration standards are accepted in the Run. The assessor verified these runs and accepts the rejection of these runs. These runs were repeated as Analytical runs 43 and 44 and were accepted.
- Out of total 3467 samples analyzed, 45 samples were reanalyzed.
- 13 samples (Test 8, Reference 5) were reanalyzed due to unacceptable internal standard response (Code B). Per SOP (b)(4) (Sample Reassays and

Reporting of Final Concentrations), the methods using a stable isotope-labelled internal standard (deuterated internal standard), samples within $\pm 70\%$ of the mean internal standard response of accepted calibration standards and quality control samples are acceptable. In the current analytical method, deuterated internal standard is used. The firm listed the samples with unacceptable internal standard and reported concentrations per SOP (*A study sample presenting an unacceptable internal standard response will be coded "B" and its concentration will be identified as NRV in the analytical repeat table of the analytical report. The repeat value will be reported in the final concentration table of the analytical report*). The assessor randomly checked raw data of IS area of some of the samples and found very different from the IS area of the other samples in the run and accepts firm's handling of reanalysis.

- One sample (Test) was reanalyzed due to the internal standard response is lower than 5% of the mean internal standard responses (Code C4). Per SOP, Code C (Incomplete Analysis), says a sample for which a concentration cannot be obtained due to technical reasons, will be coded "C (1 to 4)" and its concentration will be identified as NRV (No Reportable Value) in the analytical repeat table of the analytical report. The repeat value was reported, per its SOP. A sample from Subject (b) (6) Period 2 at 168h was reanalyzed with this reason. The assessor verified the submitted raw data and confirmed the repeat value for this sample is 33.32 pg/ml and agrees with firm's handling of this reanalysis.
- Per the bioequivalence summary tables (Table 9A), 31 samples (Test 26, Reference 5) were reanalyzed to obtain confirming value (Code G). Per Bioanalytical Report, only 29 samples were repeated with Code G, which is not consistent with that provided in the summary table. The firm will be asked about this discrepancy.

The firm provided multiple reasons for sample reanalysis under this code such as, but not limit to: when the reassay value of a diluted sample reanalyzed for code "D" (sample concentration above the upper limit of quantitation) is less than 85% of the upper limit of quantitation; and when a pre-dose sample presents a concentration higher than the lower limit of quantitation. Samples may be reassayed for additional confirmation reasons such as being part of an investigation process. The firm listed all the samples repeated under this code but did not provide specific reason for each repeat. However, out of 29 samples listed in the Bioanalytical Report, , the firm used repeated value for one sample only, the firm reported original values for the remaining 28 samples. A sample from Subject (b) (6) in Period II at 48h was reanalyzed and the 1st repeated value was reported per the SOP.

Subject	Period	Timepoint	Results Conc. (pg/mL)	Run ID	Reason For Reassay	Reported Conc. (pg/mL)	Reason For Reported Conc.
(b) (6)	2	48h	93.88, 37.70, 38.13	12, 27, 46	4	37.70	2

The assessor ran SAS using the original value (93.88 pg/mL) for this sample, the results still meet the acceptance criteria. The assessor will not pursue this issue further.

EE

Parameter	Least Squares Geometric Mean		Ratio (T/R)	90% Confidence Intervals	
	Test	Reference		Lower	Upper
LAUCT	6391.84	6750.50	0.95	90.45	99.13
LAUCI	6469.96	6845.56	0.95	90.18	99.06
LCMAX	47.53	46.78	1.02	96.62	106.88

The firm listed pre-dose repeats from 6 subjects (b) (6) under Code G, M, the original and repeated pre-dose concentrations from these six subjects are > 5% of C_{max} in Period I. In addition to these subjects, Subject (b) (6) had pre-dose concentration >5% C_{max} in Period II. All these seven subjects were excluded from PK and statistical analysis for EE (see details at section 4.1.1.4). However, the firm did not list the pre-dose repeat for subject (b) (6) in the bioanalytical report.

- **Incurred Samples Reanalysis:** A total of 231 samples (out of 3467) were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. Per incurred sample reanalysis SOP (No. 2229.00), a minimum of two samples selected per subject, per treatment and per analyte, one near the C_{max} and the other in the elimination phase at a concentration equal to or higher than the concentration of low quality control (QC1) sample. A total of 97.84% of the reanalyzed samples met the acceptance criteria of assay reproducibility within ± 20% against at least 67% of the ISR samples. The number samples needed for reanalysis per guidance is about 10% of the study samples for the first 1000 samples and approximately 5% for the remaining samples and the firm reanalyzed sufficient number of samples (224 Vs 231). The ISR study results were in line with the current FDA bioanalytical guidance (Guidance for Industry: Bioanalytical Method Validation; recommended May 2018)²⁴.

Norelgestromin (NGMN)

²⁴<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>

- Out of 24 Analytical Runs, 1 Run (No. 6) was rejected due to less than 67% of QC samples are accepted and less than 50% of QC samples at the same level are accepted in the Run. Run No. 6 containing samples Subjects 25 and 26 was rejected. The assessor verified this run and accepts the rejection of the run. These runs were repeated as Analytical runs 43 and 44 and were accepted.
- Out of total 3467 samples analyzed, 7 samples were reanalyzed. 3 samples (Test 2, Reference 1) were reanalyzed due to unacceptable internal standard response (Code B). Per the reanalysis SOP, samples which do not have IS area within $\pm 70\%$ of the mean internal standard response of accepted calibration standards and quality control samples will be reanalyzed. The firm listed these 3 samples, from Subject 02, 32 and 50, all the initial values are listed as NRV, and the repeat values are reported in the final calculations. The assessor verified raw data of IS area of these samples and accepts firm's reanalysis on these samples.
- 3 samples (Test) were reanalyzed with the reason incomplete analysis due to loss of sample during processing (Code C1). Per SOP, Code C (Incomplete Analysis), a sample loss during processing step, such as drug extraction, filtration or protein precipitation will be coded C1. These samples are from Subjects (b) (6) and (b) (6). Due to loss of these samples, the initial concentrations are listed as NRV and the repeat values are reported in the final concentration table of the analytical report. The assessor accepts the reanalysis on these samples.
- 1 sample (Reference) was reanalyzed to obtain confirming value (Code G). The firm reanalyzed pre-dose sample from Subject (b) (6) in Period 1 due to observed pre-dose concentration (512.98 pg/ml) higher than LLOQ (50 pg/mL). In reanalysis also (duplicate), the firm observed similar measurable concentrations (497.21, 515.73 pg/ml) in the pre-dose sample. Both of the original and repeated concentrations were more than 5% of C_{max} (1180.15 pg/mL) in Period I, the firm reported the original value for statistical analysis. This subject was excluded for PK and statistical analysis for NGMN. Please note this subject had pre-dose concentration >5% of C_{max} in period I for EE and also excluded from PK and statistical analysis for EE.
- Incurred Samples Reanalysis (ISR): A total of 222 samples (out of 3467) were selected for the incurred sample reproducibility test to demonstrate that results obtained from study sample analysis are reproducible. A total of 99.95% of the reanalyzed samples met the acceptance criteria of assay reproducibility within $\pm 20\%$ against at least 67% of the ISR samples. The number samples needed for reanalysis per guidance is about 10% of the study samples for the first 1000 samples and approximately 5% for the remaining samples and the firm reanalyzed sufficient number of samples, for which the firm has to select 223 samples. However, the firm performed ISR on 222 samples and justified saying that 99.5% (221 out of 222) of the samples met the acceptance criteria. The assessor accepts the firm's justification on missing one sample and believes that there is no impact on the ISR test. The

ISR study results were in line with the current FDA bioanalytical guidance (Guidance for Industry: Bioanalytical Method Validation; recommended May 2018)²⁵.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters (Assessor - Calculated)

Ethinyl Estradiol

Fasting Bioequivalence Study No. ESTN/2018/1607										
Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	pg hr/mL	6719.716	31.81	2622.92	13114.94	7279.121	38.23	2364.23	15187.40	0.92
AUCI	pg hr/mL	6797.861	31.62	2673.35	13230.48	7429.639	38.05	2401.41	15483.16	0.91
C _{MAX}	pg/mL	49.636	33.56	17.19	98.23	50.136	36.71	16.46	96.38	0.99
T _{MAX}	hr	60.000	.	36.00	144.00	84.000	.	36.00	168.00	0.71
KE	hr ⁻¹	0.032	14.94	0.02	0.04	0.032	16.52	0.02	0.04	0.98
THALF	hr	22.450	16.41	15.61	36.92	22.189	17.74	15.69	32.43	1.01

* T_{max} values are presented as median, range

Norelgestromin

Fasting Bioequivalence Study No. ESTN/2018/1607										
Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	pg hr/mL	170601.7	31.72	88743.57	339381.3	169876.7	31.21	68918.02	310808.4	1.00
AUCI	pg hr/mL	181622.8	31.61	93740.20	369868.9	182196.4	30.51	76510.06	332939.6	1.00
C _{MAX}	pg/mL	1086.181	33.09	541.07	2259.62	1087.446	31.80	429.82	2127.75	1.00
T _{MAX}	hr	84.000	.	48.00	168.00	84.000	.	60.00	168.00	1.00
KE	hr ⁻¹	0.019	22.27	0.01	0.03	0.019	22.85	0.01	0.03	0.98
THALF	hr	38.927	21.58	20.95	58.87	38.457	22.53	21.52	63.71	1.01

* T_{max} values are presented as median, range

²⁵<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated (excluding the treatment*group factor in the model)

Reference Scaled Average Bioequivalence Approach Used		☐ Yes		☒ No		
<u>Norelgestromin</u> (No of subjects completed= 79)						
Dose (150 mcg/day Transdermal System)						
Least Squares Geometric Means Ratio and 90% Confidence Intervals						
Fasted Bioequivalence Study (Study No. ESTN/2018/1607)						
Parameters	Test	N*	RLD	N*	Ratio of Geometric Means	90% C.I.
AUC _(0-t) (pg*h/mL)	163324	78	161789	76	100.95	96.87% – 105.20%
AUC _(0-∞) (pg*h/mL)	172505	78	170851	75	100.97	96.86% – 105.25%
C _{max} (pg/mL)	1035	78	1032	78	100.26	96.12% – 104.56%
*Subject (b) (6) had at least one pre-dose level of norelgestromin greater than 5% of C_{max} and as per protocol was excluded from the statistical analyses of norelgestromin. Subject (b) (6) was missing the last three time-points in Period-I (Reference) and subject (b) (6) was missing the last two time-points in Period-I (Reference) and therefore the AUC_{0-t} parameter was judged to be inadequately characterized for these subjects' periods. These subjects remained in the analysis of C_{max} and T_{max} only. Subjects (b) (6) for the Reference product for norelgestromin had terminal concentration-time values which were not log-linear or the estimated t_{1/2} was found to be physiologically implausible.						

<u>Ethinyl Estradiol</u> (No of subjects completed= 79)						
Dose (35 mcg/day Transdermal System)						
Least Squares Geometric Means Ratio and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. ESTN/2018/1607)						
Parameters	Test	N**	RLD	N**	Ratio of Geometric Means	90% C.I.
AUC _(0-t) (pg*h/mL)	6385	72	6755	70	94.52	90.19% – 99.07%
AUC _(0-∞) (pg*h/mL)	6450	72	6820	69	94.57	90.19% – 99.16%
C _{max} (pg/mL)	47.0	72	46.8	72	100.43	95.91% – 105.16%
**Subjects (b) (6) had at least one pre-dose level of ethinyl estradiol greater than 5% of C_{max} and as per protocol were excluded from the statistical analyses of ethinyl estradiol. Subjects (b) (6) for the Reference product, and subject (b) (6) for the Test product for ethinyl estradiol had						

terminal concentration-time values which were not log-linear or the estimated $t_{1/2}$ was found to be physiologically implausible. Subject (b) (6) was missing the last three time-points in Period-I (Reference) and subject (b) (6) was missing the last two time-points in Period-I (Reference) and therefore the AUC_{0-t} parameter was judged to be inadequately characterized for these subjects' periods. These subjects remained in the analysis of C_{max} and T_{max} only.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals – Assessor Calculated (excluding the treatment*group factor in the model)

Ethinyl Estradiol

Norelgestromin and Ethinyl Estradiol Transdermal System Dose: 1x 150 µg /35 µg/day Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. ESTN/2018/1607 (N=79 completed)*							
Parameter (units)	Test	N	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	6381.51	72	6750.18	72	0.95	90.33	98.95
AUC _∞ (hr *pg/ml)	6459.66	72	6845.92	70**	0.94	90.05	98.87
C _{max} (pg/ml)	46.96	72	46.76	72	1.00	95.91	105.16

* Seven subjects ((b) (6)) had at least one pre-dose level of ethinyl estradiol greater than 5% of their respective C_{max} and were excluded from the PK and statistical analyses of ethinyl estradiol.

**Subjects (b) (6) were excluded from AUC_i calculation due to missing the last three and two time-points, respectively and unreliable estimation of elimination rate constant.

Norelgestromin

Norelgestromin and Ethinyl Estradiol Transdermal System Dose: 1x 150 µg /35 µg/day Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. ESTN/2018/1607 (N=79 completed)*							
Parameter (units)	Test	N	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	162429.8	78	160920.3	78	1.01	96.90	105.15
AUC _∞ (hr *pg/ml)	173116.7	78	171855.5	76**	1.01	96.65	104.99
C _{max} (pg/ml)	1029.97	78	1027.76	78	1.00	96.03	104.58

*Subject (b) (6) had pre-dose concentration greater than 5% of C_{max} in period I with reference treatment and was excluded from the PK and statistical analyses of norelgestromin.

**Subjects (b) (6) were excluded from AUC_i calculation due to missing the last three and two time-points, respectively and unreliable estimation of elimination rate constant.

4.1.1.4.4 Additional Information for the Study

Ethinyl Estradiol

Root Mean Square Error	AUCt: 0.1639 AUCi: 0.1653 Cmax: 0.1655
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☒ Yes ☐ No Test: Median Tmax 60.000 (36.00 - 144.00) hours Reference: Median Tmax 84.000 (36.00 - 168.05) hours T/R ratio = 0.71 Please see the comments below
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☒ Yes ☐ No Please see the comments below
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☒ Yes ☐ No Please see the comments below
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	72	0.99	0.96	1.00
Reference	70	0.99	0.96	1.00
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Group Analysis Consideration

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group effect: \\cdsnas\ogds11\firmnsz\ppd\controls\98-392a.doc	☐ Yes ☒ No
If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p < 0.1)? If p ≥ 0.1, no need to consider group effect.	☐ Yes ☒ No ☐ N/A
If yes, did you use the statistical model with group effect included?	☐ Yes ☐ No ☒ N/A
If yes, specify which PK parameter(s).	

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual group meet BE criteria?	☐ Yes ☐ No ☒ N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

Norelgestromin (NGMN)

Root Mean Square Error	AUCt: 0.1521 AUCi: 0.1519 Cmax: 0.1587
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☒ No Test: Median Tmax 84.000 (48.00 - 168.00) hours Reference: Median Tmax 84.000 (60.00 - 168.00) hours T/R ratio = 1.0
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☒ Yes ☐ No Please see the comments below
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☒ Yes ☐ No Please see the comments below
Are there first measurable drug concentration as Cmax? If yes, please comment.	☐ Yes ☒ No
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Ratio of AUC0-t/AUC∞				
Treatment	n	Mean	Minimum	Maximum
Test	78	0.94	0.85	0.98
Reference	76	0.94	0.84	0.99
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below.	N/A			

Group Analysis Consideration

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group	☐ Yes ☒ No

effect: \\cdsnas\ogds11\firmnsz\ppd\controls\98-392a.doc	
If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., p < 0.1)? If p ≥ 0.1, no need to consider group effect.	☐ Yes ☒ No ☐ N/A
If yes, did you use the statistical model with group effect included?	☐ Yes ☐ No ☒ N/A
If yes, specify which PK parameter(s).	
If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual group meet BE criteria?	☐ Yes ☐ No ☒ N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

4.1.1.4.5 Comments on PK results: Inadequate

- This is a single-dose, two-treatment, two-period crossover in vivo fasting BE study conducted in 84 healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception. Subjects were dosed in 2 groups (Group I: 1 – 38 and Group II: 39 -84) with 17 days apart at the same clinical site. 5 Subjects were dropped out from the study and 79 subjects completed the study.
- Since the subjects in the study were dosed in 2 groups, the data was analyzed by the assessor using SAS program with ‘group-by-treatment (TRT*GRP) term’ in the GLM model. The TRT*GRP interaction term was tested for statistical significance at p< 0.1. The group-by-treatment interaction was found to be statistically insignificant both Ethinyl Estradiol [AUCt (p=0.8927), AUCi (p=0.9216) and Cmax (p=0.6134)] and Norelgestromin [AUCt (p=0.7107), AUCi (p=0.7181) and Cmax (p=0.8743)]. The TRT*GRP interaction term was removed from the model for the final statistical analysis as per the current Division of Bioequivalence practice.
- The firm’s statistical model also contained main effects of group, sequence, group-by-sequence, subject nested within group-by-sequence, period nested within group, treatment, and group-by-treatment. If the group-by-treatment effects were insignificant (p≥ 0.05), the group-by-treatment term was removed from the statistical model. The Group*Treatment interaction term was found to be statistically insignificant (p>0.05) for all PK parameters for EE and NGMN and was therefore removed from the model.

4.1.1.4.5.1 Ethinyl Estradiol (EE)

- For EE, 7 Subjects (Nos. (b) (6)) had at least one pre-dose level of EE greater than 5% of C_{max} and were excluded from the statistical analyses per its protocol. The removal of subject with pre-dose concentration >5% C_{max} is consistent with the BE guidance (Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, December 2013)²⁶. Therefore, 72 subjects were considered for the final PK and statistical analysis.
- Except for subject (b) (6) with pre-dose concentration > 5% of C_{max} in period II, 6 out of 7 subjects had pre-dose concentrations observed in Period I and the concentrations are up to 34.68% higher than the corresponding C_{max} values (please see the table below). It seems very unusual and raises concern about the study design and bioanalytical method. The firm will be asked to explain the reason for the pre-dose concentrations greater than 5% C_{max} for these subjects.

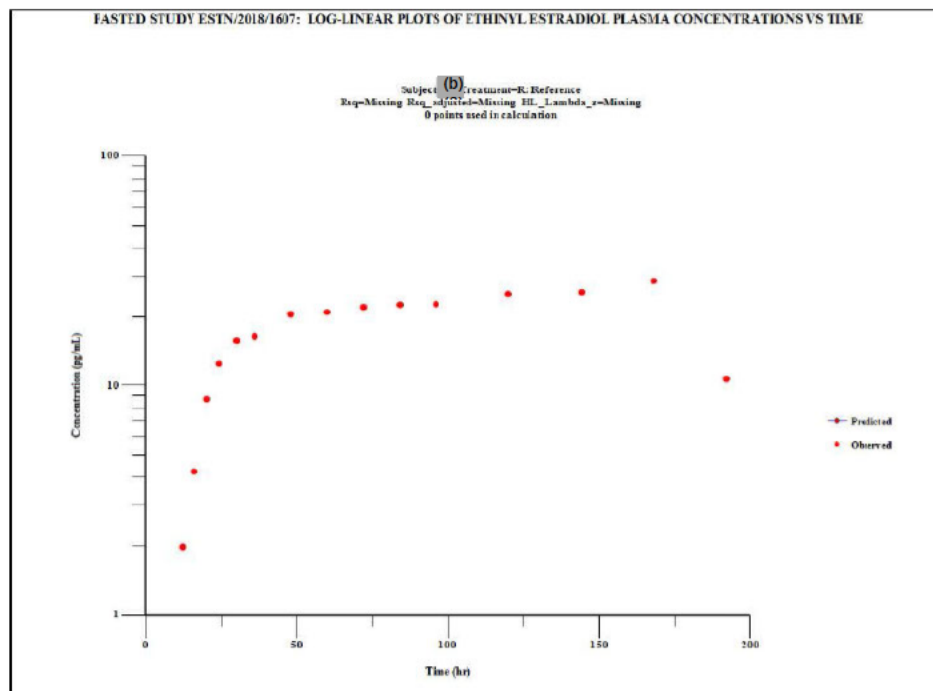
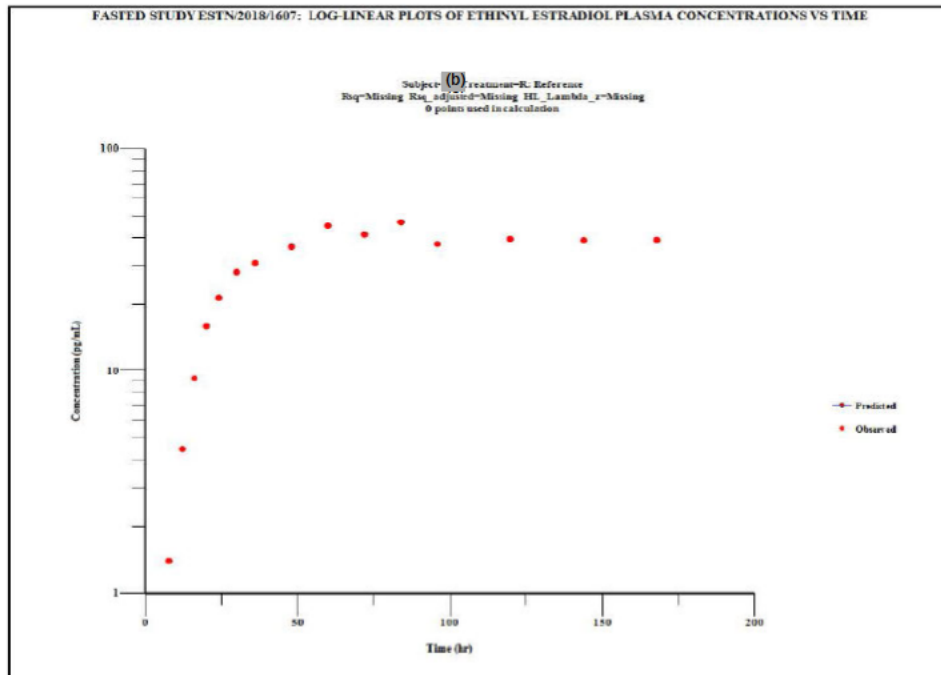
Subject ID	Period	Sequence	Treatment	Group	Pre-dose Concentration (pg/ml)	C _{max} (pg/ml)	% of C _{max}
(b) (6)	1	2	R	1	6.73	52.83	12.74
	1	2	R	1	10.82	59.70	18.12
	1	1	T	1	13.87	39.99	34.68
	1	2	R	1	7.55	41.73	18.09
	1	1	T	2	3.03	36.70	8.26
	2	1	R	2	12.94	41.80	30.96
	1	2	R	2	17.31	65.06	26.61

Additionally, 3 other subjects (Subject (b) (6) Period II, Test – 1.8 pg/ml; Subject (b) (6) Period I, Test – 1.64 pg/ml and Subject (b) (6) Period II, Test - 1.41 pg/ml) had measurable pre-dose concentrations, however, these are less than corresponding C_{max} values of these subjects. Please note that Subject (b) (6) was excluded from statistical analysis since pre-dose concentration in Period I was > 5% C_{max}. Subjects (b) (6) were included in the statistical analysis of EE.

- Subjects excluded for AUC calculation: The firm mentioned that Subject (b) (6) was missing the last three time-points in Period-I (Reference) and subject (b) (6) was missing the last two time-points in Period-I (Reference) and therefore the AUC_t parameter was judged to be inadequately characterized for these subjects' periods. These two subjects were excluded from AUC_t and AUC_i calculation in firm's statistical analysis. However, the exclusion criterium for AUC_t calculation due to missing values is not stated in the firm's study protocol. The profiles of these 2 subjects with reference treatment are presented below.

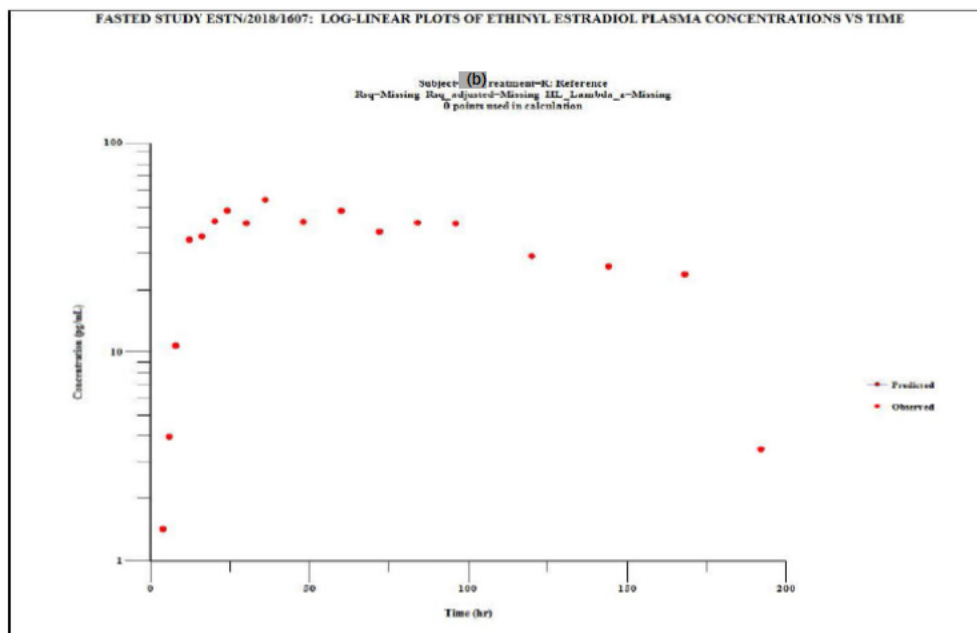
²⁶ <https://www.fda.gov/files/drugs/published/Bioequivalence-Studies-With-Pharmacokinetic-Endpoints-for-Drugs-Submitted-Under-an-Abbreviated-New-Drug-Application.pdf>

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review



- The assessor used SAS CALCKE program and included subject (b) (6) for AUCt calculation. However, since the elimination rate constant could not be reliably estimated, these two subjects were excluded in AUCi calculation.

- In addition, the firm excluded subject (b) (6) with reference treatment from AUCi calculation as the terminal concentration-time values were not log-linear or the estimated t1/2 was found to be physiologically implausible. The firm also mentioned Subject (b) (6) but this subject was already excluded from the statistical analysis due to pre-dose concentration >5% Cmax for the reference product. However, the assessor included this subject for AUCi calculation. The concentration time profile of subject (b) (6) is listed below.



- From the comments above, the firm submitted AUCt for 70 subjects (excluding Subjects (b) (6)) and AUCi for 69 subjects (excluding Subjects (b) (6)). However, the assessor calculated AUCt for 72 subjects and AUCi for 70 subjects (excluding Subjects (b) (6)). Both of the 90% CIs for LnAUCt and LnAUCi calculated by the firm and the assessor meet the BE acceptance criteria.
- After removing the above subjects as stated above, the 90% CIs for the least squares geometric means of LnAUC0-t, LnAUC∞ and LnCmax meet BE criteria of 80.00% to 125.00%.

On 03/17/2020, the Office of Pharmaceutical Quality (OPQ) held a meeting with Division of Bioequivalence (DBIII), Office of Research Standards (ORS) and Division of Clinical Review (DCR) to discuss the low loading of EE in the Anneal's test patch. Based on residual drug analysis, the OPQ team raised a question whether an additional BE study is warranted at non-abdomen site to demonstrate BE of current test product, where approximately 20% higher exposure than the abdomen site is reported. The DBIII then

discussed this issue with ORS on 04/08/2020, please refer to the meeting minutes²⁷ and following sections for further details.

A. Concerns on low loading dose of EE

- The firm loaded 0.289 mg of EE in the patch, which is 54% of the loading dose of 0.53 mg in the RS, Xulane® and ANDA 213977 (Teva), and 38.5% of EE loaded in the RLD (Ortho Evra, NDA 021180) (discontinued). Please see formulation composition at section 4.2.
- The PSG says, “*Unless otherwise justified, the ethinyl estradiol; norelgestromin TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference product, and worn for 7 days*”. Per the RS labeling, “*Apply a new patch to the upper outer arm, abdomen, buttock or back each week for 3 weeks*”, and “*Absorption of NGMN and EE following application of norelgestromin and ethinyl estradiol transdermal system to the buttock, upper outer arm, abdomen and upper torso (excluding breast) was examined. While absorption from the abdomen was slightly lower than from other sites, absorption from these anatomic sites was considered to be therapeutically equivalent.*” In the current BE study, the firm applied the TDS to abdomen.
- From the clinical studies in NDA 021180, a single dose study (No. NRGEEP-PHI-014) showed 15-20% lower exposure from the abdomen compared to other three sites (buttocks, torso and the arm, BE among themselves). The data also showed the bioequivalence between abdomen and arm/buttock/torso. A multiple dose study (No. NRGEEP-PHI-013) showed appreciably higher exposure from the abdomen than the buttock. C_{ss} values following application in the abdomen is comparable to those obtained at the other sites. Among over 70,000 patches used in the pivotal clinical trials, approximately 30 % of those were used in the abdomen and 50 % in the buttocks. The medical officer did not find any association between site of administration and the occurrence of pregnancies.²⁸ Therefore, innovator claimed that the effect of anatomical site may be considered clinically insignificant.
- Per the BE review of ANDA 200910 (current RS, Xulane from Mylan Pharmaceuticals),²⁹ in which Xulane demonstrated BE to the RLD product, Ortho Evra (NDA 021180, discontinued), Mylan applied the patch back side of the body to all the subjects in the study and had higher delivery rate of EE (53 µg/day) than

²⁷ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>, Document: A213950N000DB-MeetingMinutes01-04082020.docx

²⁸ DARRTS, NDA 021180, CHATTERJEE, DHRUBA J, 11/19/2001, REVCLINPHARM-01(General Review)

²⁹ <https://panorama.fda.gov/project/view?ID=5a682e1b002e95702462d5ae31da66df>, date 09/06/2013.

the current application (~22 µg/day) based on the residual drug analysis.³⁰ The calculated delivery rate for current test product, RLD, RS and Teva's product from three ANDAs is presented below.

	Mylan (A200910)		Amneal (A213950)		Teva (A213977)	
	RLD	Xulane	Xulane	Test	Xulane	Test
EE Loading (µg)	750	530	530	289	518	534
residual (µg) (Range)			360 (11.9 % RSD)	138 (21.9 % RSD)	267 (33 %RSD)	316 (13% RSD)
	289	159	(279 – 446)	(47 – 203)	(35-377)	(191–365)
%residual	38.5	30.00	67.92	47.75	51.54	59.18
delivered (µg)	461 (26.9% RSD)	371 (24.3% RSD)	170	151	251	218
%delivery	61.5	70.00	32.08	52.25	48.46	40.82
delivery (µg/day)	65.9	53.0	24.3	21.6	35.9	31.1
Nominal Delivery (µg/day)	35 (RLD labeling)					

From the above table, based on residual analysis, it is noticed that large difference in delivery rate among ANDAs, and also delivered amounts of EE differ significantly for RS in three ANDA BE studies. High variability is also observed in the residual data. In the RS (Xulane, ANDA 200910) BE study, EE delivered amounts in Ortho Evra (461 µg) and Xulane (371 µg) over the 7-day wearing period are ~1.9 x and 1.5 x higher than the nominal amount (245 µg (35 µg/day (labeled delivery rate) *7 days)). However, in the current test product, EE delivered amounts in Xulane (171 µg) and Test (151 µg) are <70% of the nominal amount.

OPQ raised a concern about the lower amount of EE loaded in the current test product. OPQ assumed that if Mylan's (RS, ANDA 200910) EE delivery rate derived from residual drug analysis data at a non-abdomen site is an accurate

³⁰ V:\DIVISION\BIO\BIO3\Email Communications\ANDA 213950 Norelgestromin and Ethinyl Estradiol Transdermal System, presentations.

measure of EE delivery rate $\sim 53 \mu\text{g/day}$ (RS) and $\sim 66 \mu\text{g/day}$ (RLD), the total drug load needs to be 371~462 μg per TDS to be delivered over a 7-day period (i.e., 0% residual drug). However, in Amneal's TDS (current application), the drug load is only 289 μg , and it may not be enough for 7 days of wearing period if the patch is applied at non-abdominal site. Therefore, the OPQ team raised a question whether an additional BE study is warranted at non-abdomen site to demonstrate BE of current test product.³¹ However, from a quality perspective, the lower drug loading in Amneal's proposed product complies with the Residual Drug Guidance and therefore is not a quality issue.

B. Test Formulation Development

- The firm conducted a pilot study (No. 16-VIN-0235) during product development stage, in which 34 subjects and 33 subjects were included for statistical analysis for NGMN and EE, respectively with 0.25% w/w of EE loading dose. The patch was applied at the abdomen site. The 90% CIs for Ln AUC_t, AUC_i and C_{max} met the BE criteria for NGMN, however, all the parameters failed to meet BE criteria for EE, as all the upper bounds of 90% CIs are above 125.00% (AUC_t 117.50% - 132.95%; AUC_i 117.90% - 133.80%; C_{max} 116.33% - 132.77%), the T/R ratios for AUC_t and C_{max} are close to 125.00%, and the T/R ratio for AUC_i (125.60%) exceeds 125.00%. For this reason, the firm modified the formulation, mainly with decrease (8%) in Ethinyl Estradiol loading and some other modifications in inactive ingredients. The size of the patch remained at 14.4 cm². The modified test formulation with 0.23% w/w of EE was used in 1st pivotal fasting BE study (No. 16-VIN-0236), the details of PK results and the difference between the formulations, Batch# 10103-072 (pilot) and the modified Batch# PW-ST 17042A for the 1st pivotal BE study is presented in Section 4.1.3.5.1.
- The first pivotal fasting BE study (No. 16-VIN-0236) was conducted in 59 subjects (completed) using the modified formulation, applying the patch at abdomen. The 90% CIs for Ln AUC_t, AUC_i and C_{max} met the BE criteria for NGMN, however, all these parameters failed to meet BE criteria for EE as upper limits of 90% CIs are slightly higher than 125.00% (AUC_t 113.56 – 125.55%; AUC_i 113.41 – 125.49%; C_{max} 114.59 – 127.06), and T/R ratios are close to 120% (119.29~120.66%). After the failure of this first pivotal BE study, the firm reformulated the formulation again with further modifications. The firm reduced additional 5% in EE load and also reduced the patch size by about 13%, 14.4 cm² to 12.5 cm², in order to achieve bioequivalence with the RS product. The final test formulation contains 0.22% w/w of EE. Please refer to Section 4.1.3.5.1. for the comparison of 2 formulations, one used in 1st pivotal study (Batch No. PWST-17042A) and the final formulation used in the second (current) passed pivotal study (Batch No. PW-ST-18020A) and PK results.

³¹ V:\DIVISION\BIO\BIO3\Email Communications\ANDA 213950 Norelgestromin and Ethinyl Estradiol Transdermal System, Residual Drug - Ortho Evra ANDAs OPQ 03172020.pptx

- Due to high EE exposure observed in the pilot and 1st pivotal studies, the firm

(b) (4)

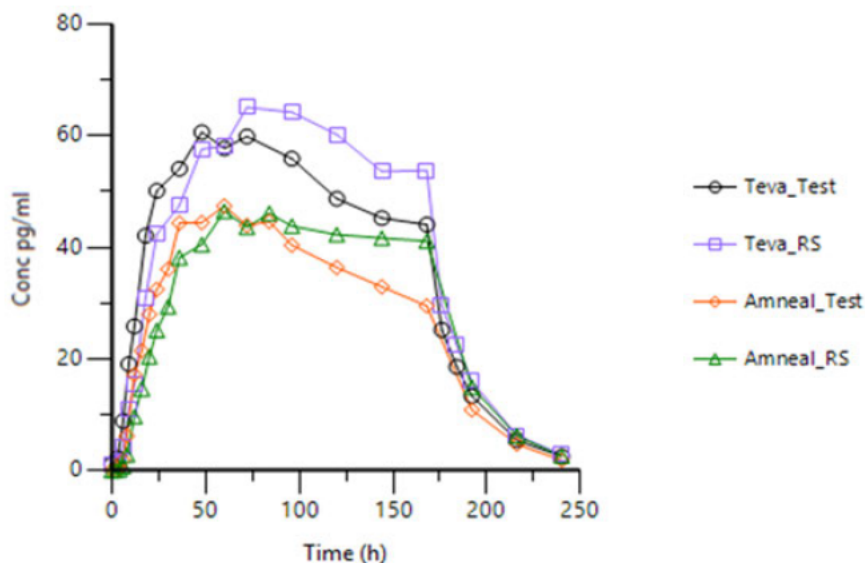
The firm stated that Amneal's generic version of Norelgestromin and Ethinyl Estradiol TDS was designed and developed using an appropriate scientific approach to achieve bioequivalence while minimizing the initial drug load in the test patch without affecting the patch pharmacokinetic performance. The formulation strategy of reducing the initial drug load as compared to RS enabled a reduction in Residual Drug and Residual Enhancer remaining in the test patch after use.

Based on firm's residual analysis³², about 48% residual EE left in the Amneal's patch with abdomen administration. Based on NDA studies cite above, absorption from abdomen is only about 15~20% less than other sites, so it is expected that EE amount loaded in the current TDS to be sufficient even if the patch has higher absorption at non-abdominal site. However, high variability is observed in residual drug analysis data and the residual analysis may not reflect actual rate of in vivo drug release for EE.

C. PK profile comparison

- From the mean concentration vs time profiles for EE submitted by the firm, it was noticed that there are differences in PK profiles over 7 day period of TDS application. For this reason, the assessor also compared the concentration time profiles between current ANDA and ANDA 213977 (Teva Pharmaceuticals) as shown below. The RS and Teva's test product in ANDA 213977 showed higher C_{max} and exposure than the current ANDA. The shape of the profiles between RS and Teva TDS product looks similar. However, there is a significant drop in mean concentrations in Amneal's test product compared to Xulane® between 72~168 hours. It raised concern whether the slower release observed in the test product is due to insufficient loading dose of EE after 3-days of application.

³² <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\pwy-19-mis-066\study-report-body-pdf.pdf>

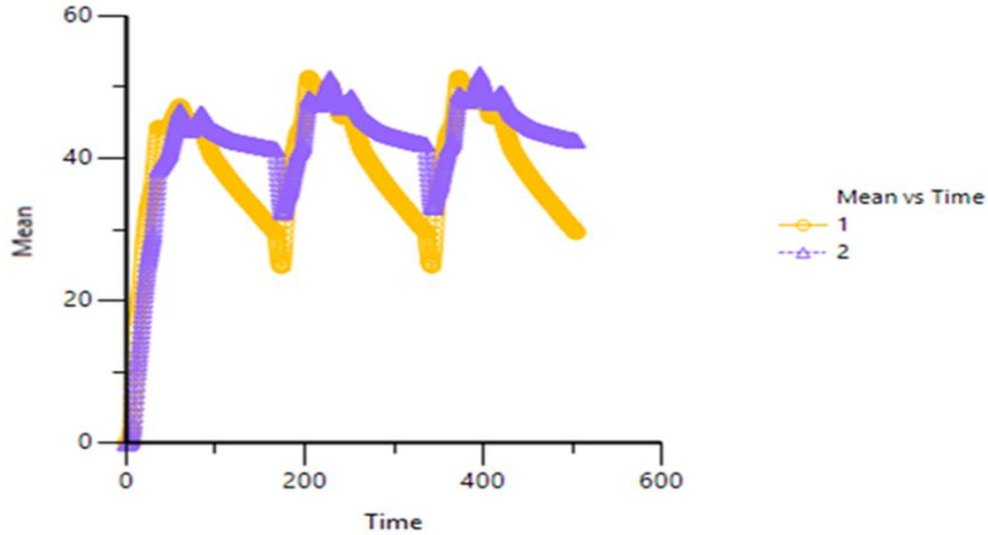


- For this reason, the assessor conducted partial AUCs using Phoenix software from 0-72, 72-168 hrs and compared with 0-168 hrs. The results are presented below.

Dependent	TestGeoLSM	RefGeoLSM	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
Ln(AUC0-168)	5678.83	5782.89	98.20	93.25	103.41
Ln(AUC0-72)	2265.80	1928.67	117.48	110.08	125.38
Ln(AUC72-168)	3382.04	3824.54	88.43	84.27	92.80

The above results indicate pAUC0-168 and pAUC72-168 met BE criteria. However, that AUC0-72 has a T/R ratio of 117.48% with 90% upper CI slightly exceeding the acceptance upper limit of 125.00. The results showed higher exposure for the test product from 0-72 hrs than the RS.

- In addition, the assessor conducted multiple dose/steady state simulation for the application of 3 patches, each patch applied every 168 hrs (7 days). The concentration vs time plot for simulation and PK parameters (AUC and Cmax) for 3rd dose are presented below.



Treatment 1: Test; Treatment 2: Reference

Dependent	TestGeoL SM	RefGeoLS M	Ratio_ %Ref_	CI_90_Lower	CI_90_Upper
Ln(AUC_TAU)	6198.29	6506.34	95.27	90.54	100.24
Ln(AUClast)	17768.22	18995.79	93.54	88.73	98.61
Ln(Cmax)	48.56	47.51	102.20	96.92	107.77
Ln(Cmin)	22.41	26.30	85.21	79.53	91.30

- The 90% CIs for LnAUCtau, LnAUClast, Ln Cmax are within the acceptable BE limits, but the lower limit of 90% CI for LnCmin is slightly less than 80%.
- Even though the difference in concentration-time profiles from 72-168 hours in current ANDA is justified with calculation of partial AUCs and steady state simulation, due to the observed differences in concentration time profiles between test and reference products between 72-168 hrs, the firm will be asked to address our concern whether the loading amount is sufficient to deliver EE throughout 7-day wear period of the test patch. In addition, based on NDA studies, absorption of NGMN and EE during patch application on the abdomen was approximately 20% less than that for the other three sites i.e., buttock, arm, and torso, the firm will be

asked to provide justification that the loading amount of EE is sufficient for a non-abdominal site of administration as well.

Based on discussion with ORS³³, DBIII will sent a consult request to Division of Quantitative Methods & Modeling (DQMM) to (i). estimate the amount of drug delivered by the test and reference TDS on a non-abdominal site (i.e., back) based upon a deconvolution of the PK data, and (ii) predict the PK across the back (as a non-abdominal site) based on diffusion parameters obtained for the test product from the abdomen utilizing a physiologically based model.³⁴ Those data could use as the supporting evidence to eliminate the need of another BE study at a non-abdominal site.

D. Justification for Tmax difference

- The median (range) Tmax for the test and reference products for EE is 60.000 (36.00 - 144.00) hours and 84.000 (36.00 - 168.05) hours, respectively, with a T/R ratio of 0.71. Per the Clinical Pharmacology section of the RS label, “*Following a single application of norelgestromin and ethinyl estradiol transdermal system, both NGMN and EE reach a plateau by approximately 48 hours*”. The Tmax of the current test product (60 hrs) is closer to the finding in the label compared to the Reference product in the current study. During the fasting study, for the analysis of norelgestromin and ethinyl estradiol, blood samples were collected at the time points of pre-dose, 02.00, 04.00, 06.00, 08.00, 12.00, 16.00, 20.00, 24.00, 30.00, 36.00, 48.00, 60.00, 72.00, 84.00, 96.00, ..., and 240.00 hours. Based on this sampling schedule, only one sample at 72 hrs was collected between 60 hrs (test Tmax) and 84 hrs (RS’ Tmax). Since the measurement of Tmax depends on the sampling time points, the above Tmax difference can be attributed to firm’s sampling time schedule to some extent. Also, for both test and reference PK profiles of EE, there are double peaks observed for Cmax, which might have also contributed to the difference in Tmax between test and reference products. Thus, the difference in Tmax determined within this time period appeared to be due to the data variability rather than formulation differences.
- Based on the NDA review, variability in the Tmax for ethinyl estradiol was observed in different conditions and in different studies³⁵.

³³ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>, Document: A213950N000DB-MeetingMinutes01-04082020.docx

³⁴ <https://panorama.fda.gov/task/view?ID=5ebab3ac0010e1c8cd8a57fbf4dcef7e>

³⁵ DARRTS, NDA 021180, CHATTERJEE, DHRUBA J, 11/19/2001, REVCLINPHARM-01(General Review)

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

Table: Mean (SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of an EVRA™ Contraceptive Patch of 17d-NGM and EE Under Conditions Found in a Health Club (Study NRGEEP-PHI-015)						
Parameter	Combination	Cool Water	Normal	Sauna	Treadmill	Whirlpool
EE						
t _{max} (h)	42.9 (17.6)	84.0 (48.1)	86.9 (48.5)	65.4 (35.3)	60.9 (36.8)	76.5 (52.0)
C _{max} (pg/mL)	89.9 (32.2)	63.9 (18.1)	64.5 (21.6)	85.4 25.8	81.3 21.2	80.8 (39.8)
C ₅₅ (pg/mL)	59.3 (19.0)	52.3 (16.8)	53.0 (18.7)	61.7 (20.0)	60.8 (17.0)	55.2 (16.8)
AUC _{0-168h} (pg·h/mL)	10343 (3293)	8186 (2458)	8237 (3047)	10172 (3428)	10378 (2534)	8987 (2749)
AUC _{0-240h} (pg·h/mL)	11132 (3600)	9109 (2796)	9055 (3377)	11155 (3631)	11246 (3034)	9716 (2865)
AUC _{0-∞} (pg·h/mL)	11229 (3612)	9225 (2727)	9416 (3131)	11679 (3867)	11345 (3026)	9807 (2875)
t _{1/2} (h)	15.2 (3.48)	14.9 (3.58)	15.0 (2.67)	25.7 (30.9)	17.7 (9.51)	18.0 (7.34)
N	12	12	29	12	12	11

Table: Mean (SD) Pharmacokinetic Parameters Obtained from 36 Women Wearing the 20-cm² Seven-Day EVRA™ Patch at Different Application Sites (Study NRGEEP-PHI-004)				
Parameter	Abdomen	Arm	Buttock	Torso
EE				
C _{max} (pg/mL)	58.7 (19.9)	69.5 (20.6)	66.3 (23.9)	71.2 (32.2)
t _{max} (h)	56 (27.3)	57.8 (32.7)	52.7 (32.4)	56.2 (26.6)
C ₅₅ (pg/mL)	46.6 (14.0)	57.0 (14.9)	54.0 (16.5)	57.1 (20.3)
AUC _{0-168h} (pg·h/mL)	7163 (2211)	8751 (2272)	8391 (2622)	8599 (3161)
AUC _{0-240h} (pg·h/mL)	7766 (2332)	9540 (2437)	9189 (2755)	9523 (3354)
t _{1/2} (h)	16.1 (3.02)	16.4 (3.47)	18.1 (6.43)	17.1 (3.81)

In NDA study No. NRGEEP- PHI-015, the Tmax varies between 60.9 to 86.9 hrs in different conditions. In the study No. NRGEEP-PHI-004, it is observed between 52.7 to 57.8 hrs at different application sites. Tmax at abdomen site is 56 hours. In addition, per the BE study of the ANDA 200910 (RS), there is a significant difference in Tmax between test and RLD product with a T/R ratio of 1.25 as shown below, which was justified and accepted. In ANDA 213977 (pending), there is no significant difference in Tmax between test and reference products (T/R ratio 0.83). The median Tmax of test product in current ANDA 213950 is the same as that in ANDA 213977.

Median Tmax, range and ratio for Ethinyl Estradiol in fasting BE study

ANDA No. /administration site	Tmax – Test (hrs) (Range)	Tmax – RLD/RS (hrs) (Range)	Tmax ratio (T/R)
200910 (RS) Back site	120 (48 – 170)	96 (48 – 170)	1.25
213977 (Teva) Abdomen	60.00 (18.00 - 168.00)	72.18 (48.00 - 168.00)	0.83
213950 (Current application) Abdomen	60 (36.00 - 144.00)	84 (36 – 168.05)	0.71

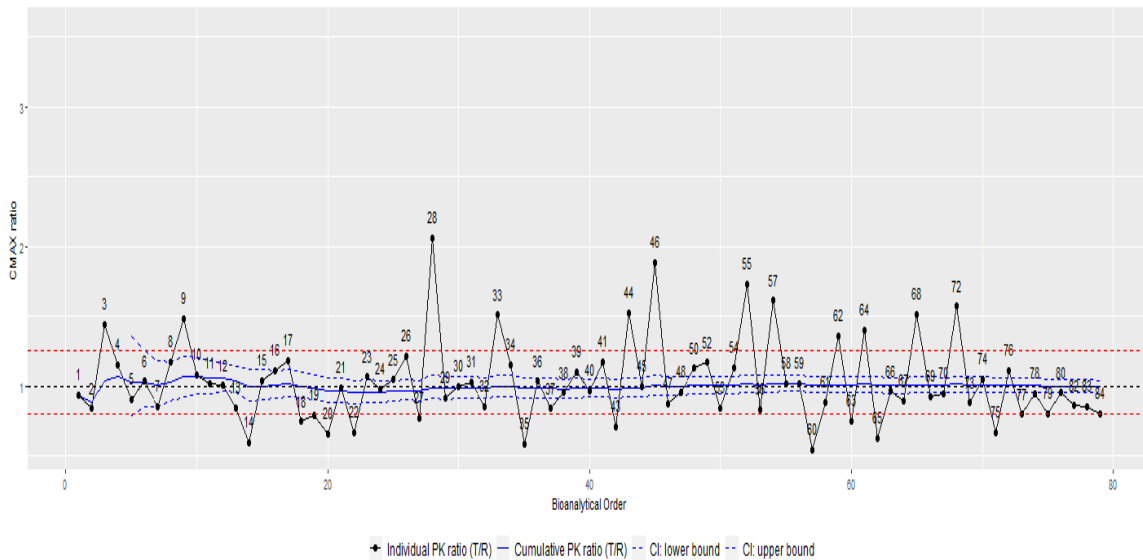
- In addition, the assessor conducted simulation study using Phoenix software with 3 patches applied every 168 hours (7 days). Per the RLD label says, “Pooled data from the 3 clinical studies have demonstrated that steady state is reached within 2 weeks of application”. As the 4th week is patch free day, the assessor did not use

simulation study beyond 3 weeks of application. From the steady state simulation, the difference of Tmax remains the same.

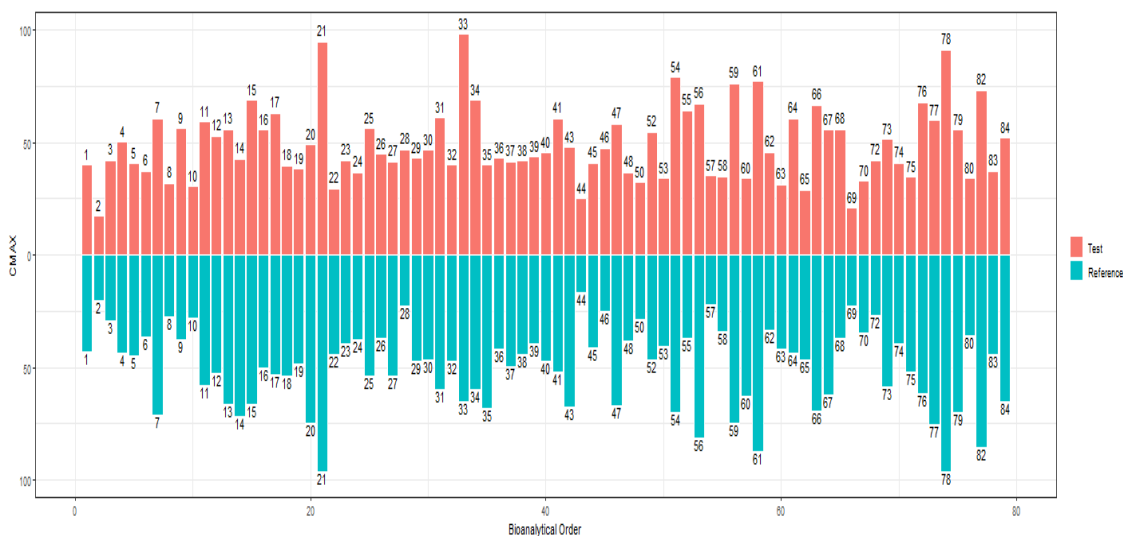
- Therefore, the apparent difference observed in the median Tmax between the test and reference treatments is not considered significant and is acceptable.

E. PK profile similarity analysis

- DABERS (Data Anomalies in Bioequivalence R Shiny app) tool: Similarity of PK profiles or/and unusual PK trend (i.e., distinct sub-groups in the study) were identified in the some ANDAs using Synchron as analytical site. Although Synchron is the clinical site in the current application, this analysis is still conducted for the current application, which can be served as a negative control.
- To find out any data integrity issues in the fasting BE study, the assessor conducted Correlation Analysis, Dissimilarity Factor Analysis and Weighted Difference analysis on the individual PK profiles. From these analyses, no common pairs were identified for EE from all the 3 calculation methods and no unusual trend was observed between 2 groups of subjects' data. The data files including summary files are attached in Section 4.4.2.
- Cmax Trend Analysis of EE



ANDA 213950
Single-Dose Fasting Bioequivalence Study Review

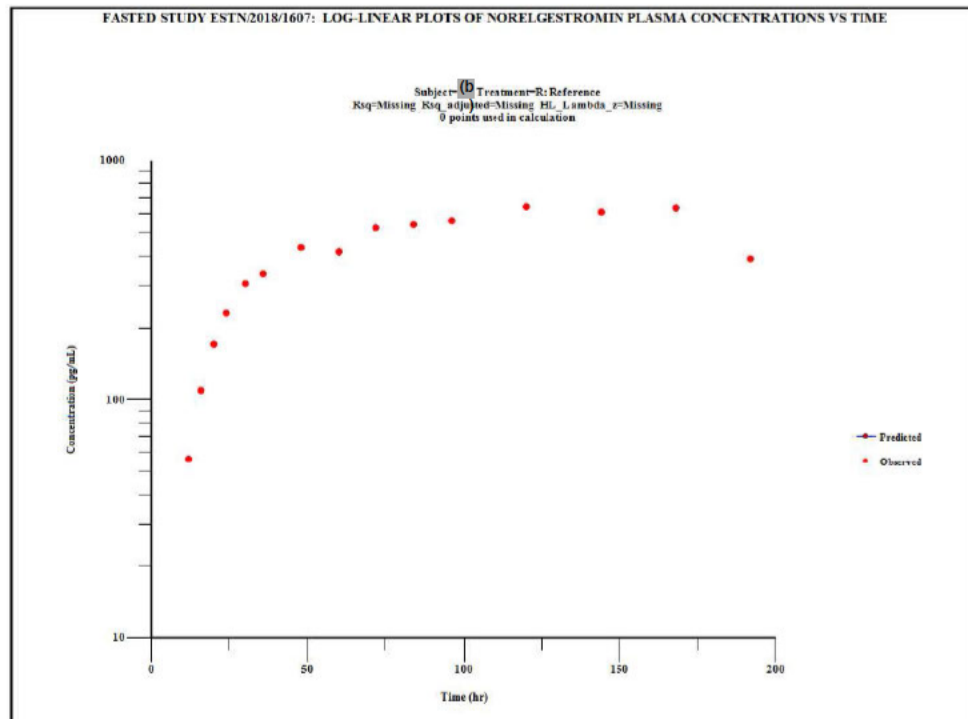
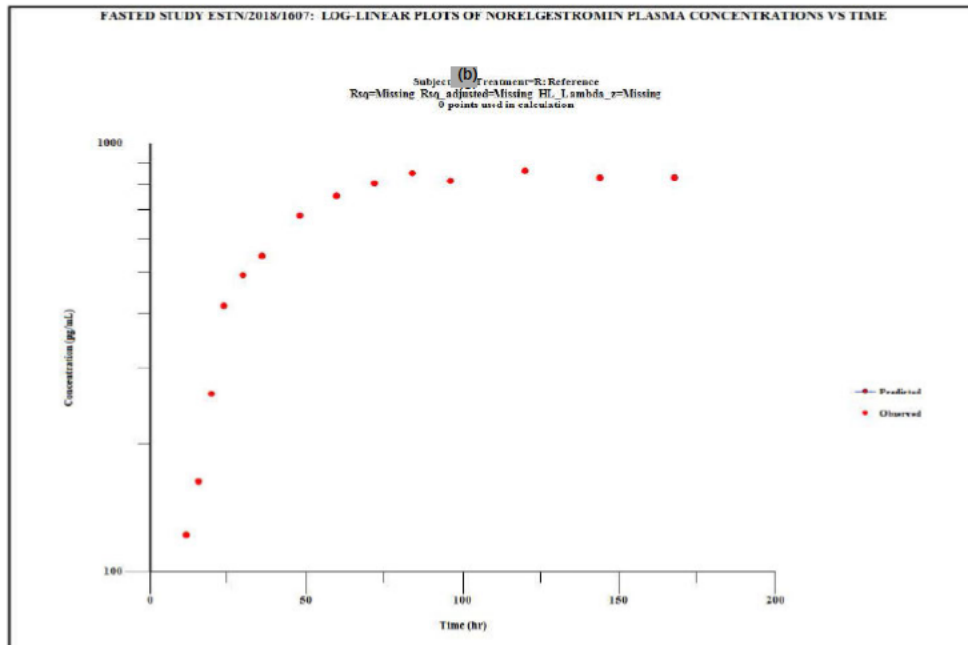


- Unusual Cmax trend is not observed. However, there are some individual subject profiles with T/R ratio greater than 2 (Subject (b) (6) or close to 2 (Subject (b) (6)). Both subjects do not have unusual concentrations for either test or reference treatments, however, the concentrations with test product administration are much higher compared to the concentrations with reference product in the same subject. The assessor also checked if there were any anomalies in CRF and analytical results including checking the order of sample analysis for potential clinical and analytical issues, but could not find any suspicious data.

4.1.1.4.5.2 Norelgestromin (NGMN)

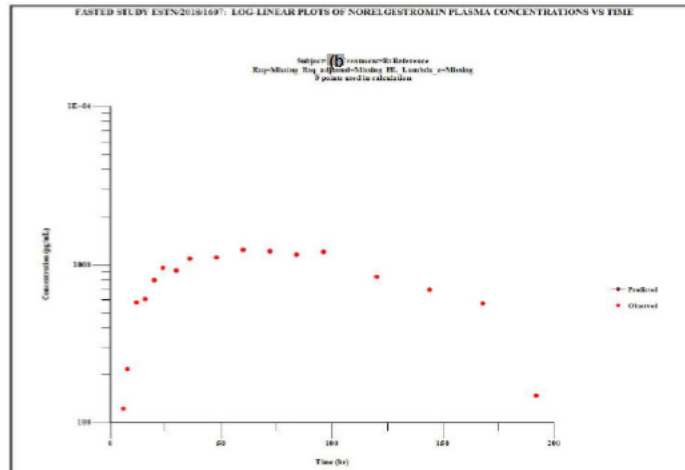
- For NGMN, Subject (b) (6) had a pre-dose concentration greater than 5% of Cmax in period I with reference treatment. As per study protocol, this subject was excluded from the statistical analysis of NGMN and a total of 78 subjects were included in final statistical analysis. No other subject has any pre-dose concentrations. Since the pre-dose concentration in period I for subject (b) (6) is 44% of the Cmax, the firm will be asked to provide explanation.
- Subjects excluded for AUC calculation: The firm mentioned that Subject (b) (6) was missing the last three time-points in Period-I (Reference) and subject (b) (6) was missing the last two time-points in Period-I (Reference) and therefore the AUCt parameter was deemed to be inadequately characterized for these subjects' periods, these two subjects were excluded from AUCt and AUCi calculation. The exclusion criteria for AUCt calculation due to missing values was not stated in the firm's study protocol. The profiles of these 2 subjects are presented below.

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review



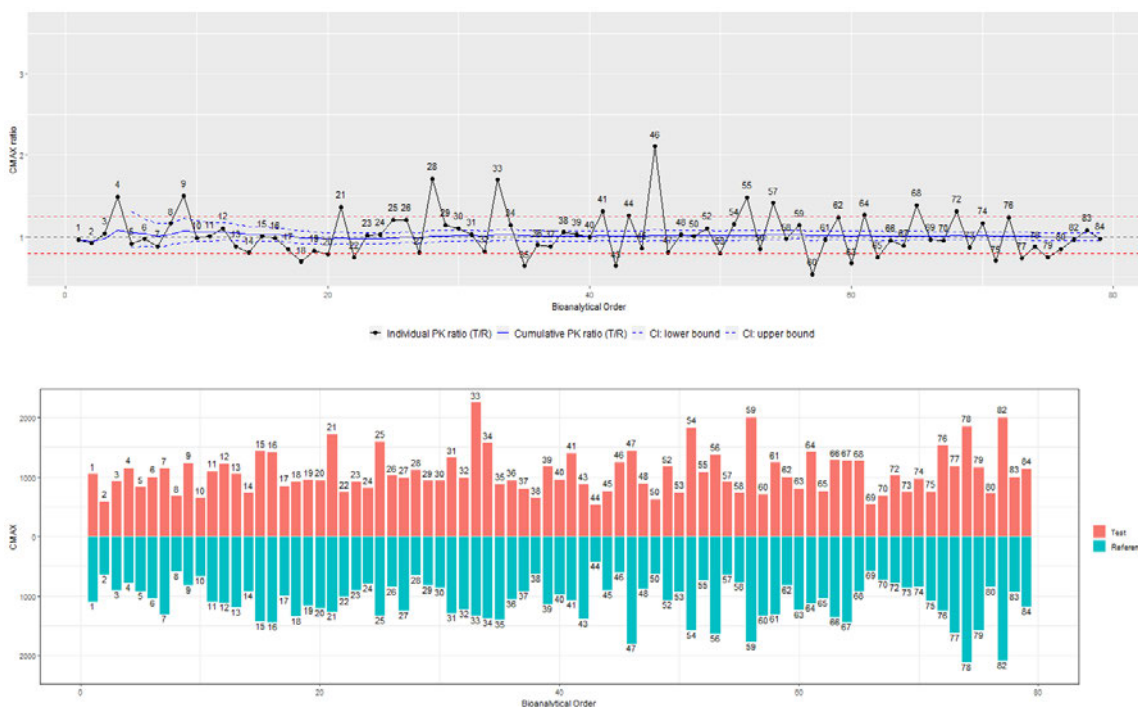
- However, the assessor includes subject (b) (6) and (b) (6) for AUC_t and C_{max} calculation, but not for AUC_i calculation due to unreliable estimation of elimination rate constant.
- In addition, the firm mentioned that terminal concentration-time values were not log-linear or the estimated t_{1/2} was found to be physiologically implausible for

subject (b) (6) (the firm also mentioned Subject (b) (6) but this subject was already considered above) for the reference product. However, the assessor included this subject for AUC_i calculation. The concentration time profile of subject (b) (6) is listed below.



- From the above comments about exclusion of the subjects in statistical analysis, the firm submitted AUC_t for 76 subjects (excluding subjects (b) (6)) and AUC_i for 75 subjects (excluding Subjects (b) (6)). However, the assessor calculated AUC_t for 78 subjects and AUC_i for 76 subjects (excluding Subjects (b) (6)). Both of the 90% CIs for LnAUC_t and LnAUC_i calculated by the firm and the assessor meet the BE acceptance criteria.
- The pharmacokinetic parameters, LnAUC_t, LnAUC_i and LnC_{max} for NGMN fall within BE criteria of 80.00% to 125.00%. The results submitted by the firm are similar to the results obtained by the assessor.
- The median (range) T_{max} for the test and reference products is 84.000 (48.00 - 168.00) hours and 84.000 (60.00 – 168.03) hours, respectively, with a T/R ratio of 1.0 for NGMN.
- DABERS tool: Similar to EE, the assessor conducted Correlation Analysis, Dissimilarity Factor Analysis and Weighted Difference analysis on the individual PK profiles for NGMN. From these analyses, one common pair (subj23s2p1tB vs subj30s2p1tB) was identified using 3 methods, the assessor did not see any unusual PK trend over the two groups of subjects either. The data files including summary files are attached in Section 4.4.2.
- C_{max} Trend Analysis of NGMN

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review



- Unusual Cmax trend is not observed. However, there are some individual subject profiles with T/R ratio greater than 2 (Subject (b) (6) or close to 2 (Subject (b) (6)). Subjects (b) (6) do not have unusual concentrations for either test or reference treatments. Subject (b) (6) had relatively very high concentrations (highest in Cmax) and exposure with test treatment and normal concentrations with reference treatment. The concentrations with test product administration are much higher compared to the concentrations with reference product in the same subject, which resulted in high T/R ratio. The assessor also checked if there were any anomalies in CRF and analytical results including checking the analytical order of sample analysis for potential clinical and analytical issues, but could not find any suspicious data.
- The pharmacokinetic results for NGMN are inadequate.

Overall Comment

Was the fasting bioequivalence study acceptable? Inadequate

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Ethinyl Estradiol

Time (hr)	Test (n=72)		Reference (n=72)		Ratio
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.04	597.50	0.00	.	.
2.00	0.06	485.02	0.00	.	.
4.00	0.35	310.00	0.17	293.99	2.07
6.00	1.87	136.11	0.78	168.64	2.41
8.00	6.21	98.26	2.86	107.98	2.17
12.00	17.19	70.18	9.66	83.56	1.78
16.00	21.47	53.54	14.64	70.19	1.47
20.00	27.98	49.06	20.38	62.34	1.37
24.00	32.45	46.18	25.09	55.70	1.29
30.00	36.09	44.50	29.37	52.55	1.23
36.00	44.35	39.79	38.15	46.87	1.16
48.00	44.42	36.18	40.47	43.42	1.10
60.00	47.40	33.73	46.44	38.96	1.02
72.00	43.91	32.61	43.61	39.04	1.01
84.00	44.60	32.31	46.09	36.42	0.97
96.00	40.37	33.13	43.79	38.05	0.92
120.00	36.36	31.34	42.26	38.79	0.86
144.00	32.91	30.52	41.63	36.19	0.79
168.00	29.50	30.33	41.09	38.83	0.72
192.00	10.87	40.86	14.94	48.65	0.73
216.00	4.73	50.79	6.22	59.98	0.76
240.00	1.83	74.92	2.56	78.26	0.72

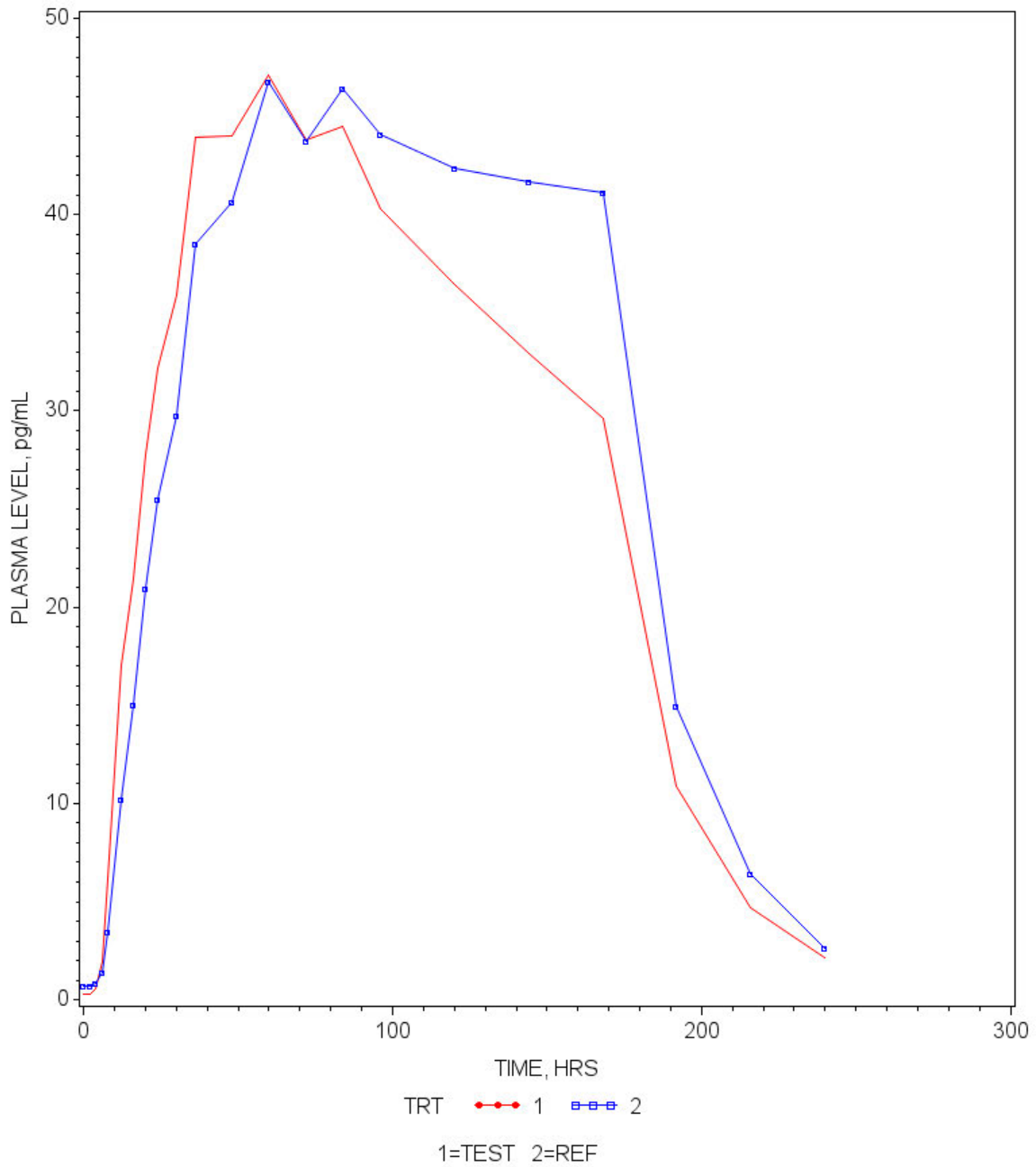
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(Norelgestromin)

Time (hr)	Test (n=78)		Reference (n=78)		Ratio
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
2.00	0.00	.	0.00	.	.
4.00	7.30	351.59	0.68	883.18	10.77
6.00	44.83	152.38	19.71	194.02	2.27
8.00	134.48	87.19	78.85	97.64	1.71
12.00	305.84	62.98	216.85	68.38	1.41
16.00	349.01	50.26	285.19	55.05	1.22
20.00	457.36	49.27	386.63	54.20	1.18
24.00	590.78	45.71	513.46	47.38	1.15
30.00	670.24	44.96	596.82	44.97	1.12
36.00	818.88	41.87	753.43	43.57	1.09
48.00	906.80	38.67	853.26	38.50	1.06
60.00	1004.29	35.67	976.81	35.60	1.03
72.00	1015.27	33.66	994.61	35.21	1.02
84.00	1038.85	32.91	1038.31	31.62	1.00
96.00	999.73	32.31	1029.28	32.48	0.97
120.00	967.38	31.10	984.40	30.17	0.98
144.00	910.88	29.94	942.12	28.62	0.97
168.00	847.38	29.91	878.07	28.71	0.97
192.00	469.76	35.85	489.97	32.74	0.96
216.00	294.46	41.11	294.44	41.06	1.00
240.00	177.75	49.82	182.64	46.60	0.97

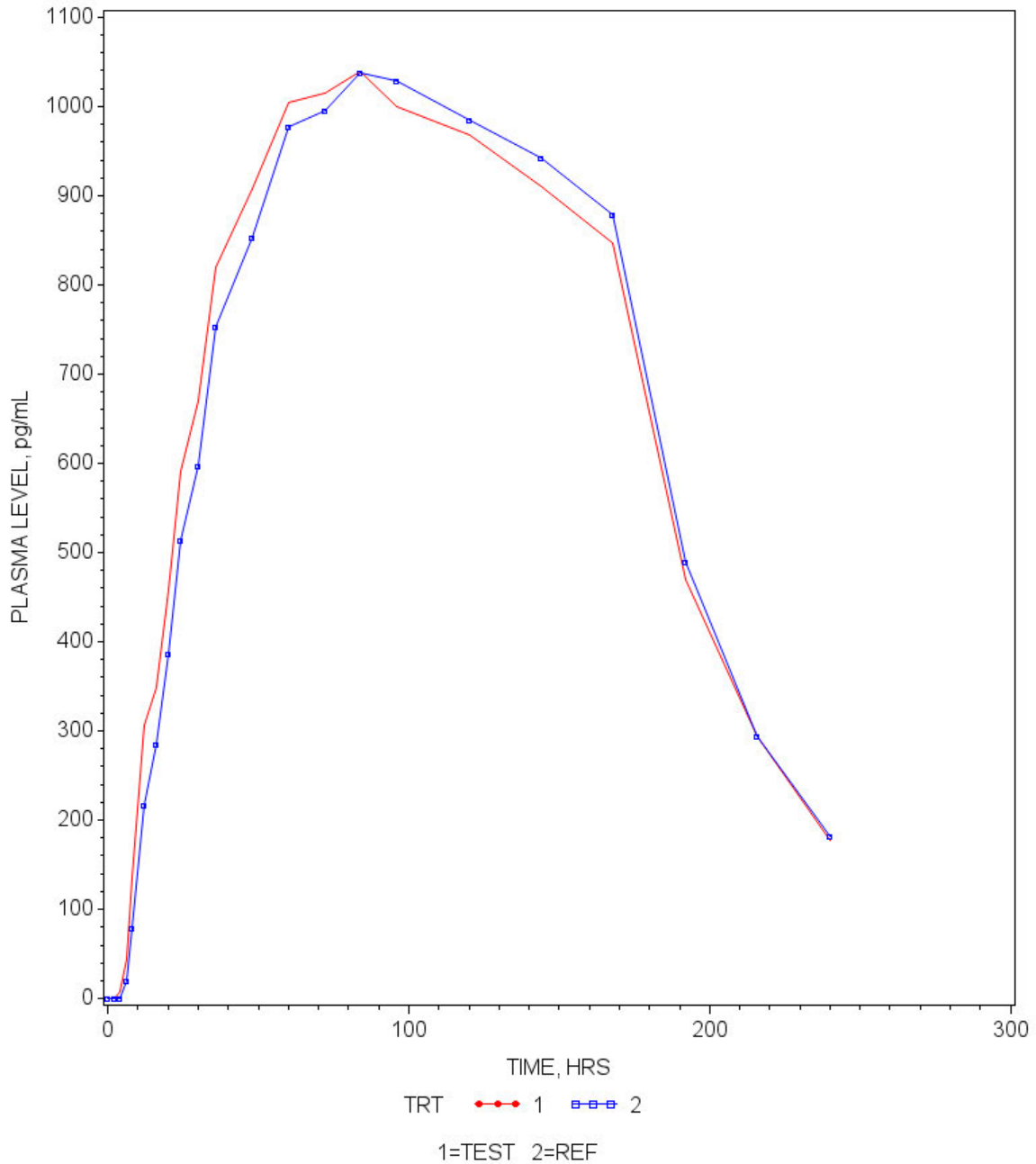
Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Ethinyl Estradiol)

PLASMA Ethinyl Estradiol LEVELS
Norelgestromin and Ethinyl Estradiol TDS, ANDA 213950
UNDER Fasting CONDITIONS
DOSE= 1 TDS



Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Norelgestromin)

PLASMA Norelgestromin LEVELS
Norelgestromin and Ethinyl Estradiol TDS, ANDA 213950
UNDER Fasting CONDITIONS
DOSE= 1 TDS



4.1.2 Single-Dose Failed Pivotal Fasting Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	16-VIN-0236			
Study Title	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting conditions.			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location	Not Applicable			
Study Report	Not Applicable			
Validation Report	Not Applicable			
Bioanalytical Report	Not Applicable			
Clinical Site (Name, Address, Phone #, Fax #)	Veeda Clinical Research Pvt. Ltd. Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India Tel. No.: +91-79-30013000; Fax No.: +91-79-30013010			
Principal Clinical Investigator (Name, Email)	Dr. Ronak Prajapati, M.D. (Pharmacology) ronak.prajapati@veedacr.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Principal Analytical Investigator (Name, Email)				
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	a) Ethinyl estradiol Group 1: 92 days (20-FEB-2018 to 23-MAY-2018) Group 2: 77 days (06-MAR-2018 to 22-MAY-2018) Group 3: 74 days (15-MAR-2018 to 28-MAY-2018) 17-desacetylnorgestimate Group 1: 83 days (20-FEB-2018 to 14-MAY-2018) Group 2: 71 days (06-MAR-2018 to 16-MAY-2018) Group 3: 68 days (15-MAR-2018 to 22-MAY-2018)			

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

	b) -80°C (Receipts of 06 and 20-APR-2018) -20°C (Receipt of 03-MAY-2018)
Long-Term Storage Stability (LTSS) Coverage (no. days @ °C) temp	Ethinyl estradiol: 95 days at -20°C (fortified with 17-desacetylnorgestimate) 17-desacetylnorgestimate: 909 days at -20°C (fortified with ethinyl estradiol)
LTSS Data Location	Not Applicable

4.1.2.1.2 Product Information

Product	Test	Reference		
Treatment ID	T	R		
Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day	Xulane® (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day		
Manufacturer	Anneal Pharmaceuticals LLC	Distributed by Mylan Pharmaceuticals Inc. Morgantown, WV26505 U.S.A.		
Batch No./Lot No.	PW-ST-17042A (Batch No.)	3086481 (Lot No.)		
Manufacturing Date	05 Dec 2017	Not applicable		
Expiration Date	Not applicable	Mar 2019		
Strength	150/35 mcg per day	150/35 mcg per day		
Dosage Form	Transdermal Patch	Transdermal Patch		
Bio-batch Size	(b) (4) Feet	Not Applicable		
Production Batch Size	Not Applicable	Not Applicable		
Potency	Norelgestromin - 99.6 %	Norelgestromin - 100.1 %		
	Ethinyl Estradiol - 98.5 %	Ethinyl Estradiol - 97.3 %		
Content Uniformity (mean, %CV) - Ethinyl Estradiol	No. of units, n = 10	No. of units, n = 10		
	Min	(b) (4)		
	Max	(b) (4)		
	Mean	98.9	Mean	97.0
	AV	3.1	AV	3.2
Content Uniformity	No. of units, n = 10	No. of units, n = 10		
	Min	(b) (4)		

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

(mean, %CV) Norelgestromin	Max	(b) (4)		
	Mean	100.8	Mean	99.8
	AV	3.0	AV	1.1
Dose Administered	150/35 mcg per day for 07 days		150/35 mcg per day for 07 days	
Route of Administration	Topical		Topical	

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. 16-VIN-0236			
		Treatment Groups	
		Test Product (T) N = 59	Reference Product (R) N = 59
Age (years)	Mean ± SD	29.51 ± 3.67	29.51 ± 3.67
	Range	21.00 – 34.00	21.00 – 34.00
Age Groups	< 18	00 (00.00%)	00 (00.00%)
	18 – 40	59 (100.00%)	59 (100.00%)
	41 – 64	00 (00.00%)	00 (00.00%)
	65 – 75	00 (00.00%)	00 (00.00%)
	> 75	00 (00.00%)	00 (00.00%)
Sex	Male	00 (00.00%)	00 (00.00%)
	Female	59 (100.00%)	59 (100.00%)
Race	Asian	59 (100.00%)	59 (100.00%)
	Black	00 (00.00%)	00 (00.00%)
	Caucasian	00 (00.00%)	00 (00.00%)
	Hispanic	00 (00.00%)	00 (00.00%)
	Other	00 (00.00%)	00 (00.00%)
BMI (Kg/m ²)	Mean ± SD	25.65 ± 3.18	25.65 ± 3.18
	Range	19.90 – 29.72	19.90 – 29.72
Height (cm)	Mean ± SD	153.40 ± 5.29	153.40 ± 5.29
	Range	138.00 – 167.00	138.00 – 167.00
Weight (Kg)	Mean ± SD	60.36 ± 8.09	60.36 ± 8.09
	Range	46.50 – 77.50	46.50 – 77.50

4.1.2.2.2 Dropout Information

Study No. 16-VIN-0236				
Subject No	Reason for dropout/replacement	Period	Replaced	Replaced with
(b) (6)	Subject withdrawn due to adverse event Date & Time: 22 Feb 2018 & 08:48 Last treatment: T	01	NO	NA
	Subject did not report to the facility Date & Time: 21 Mar 2018 & 23:20 Last treatment: R	02	NO	NA
	Subject withdrew consent Date & Time: 22 Feb 2018 & 11:45 Last treatment: R	01	NO	NA
	Subject did not report to the facility Date & Time: 21 Mar 2018 & 23:22 Last treatment: R	02	NO	NA
	Subject withdrew consent Date & Time: 06 Mar 2018 & 00:18 Last treatment: NA	01	NO	NA

4.1.2.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study Study No. 16-VIN-0236	
	Test Product (T)	Reference Product (R)
Vascular disorders		
Thrombophlebitis	01 (01.67 %)	00 (00.00 %)
Gastrointestinal disorders		
Vomiting	02 (03.33 %)	00 (00.00 %)
Abdominal pain	00 (00.00 %)	01 (01.61 %)
Swelling of lower lip	00 (00.00 %)	01 (01.61 %)
Nervous system disorders		
Headache	01 (01.67 %)	01 (01.61 %)
General disorders and administration site conditions		
Fever	00 (00.00 %)	01 (01.61 %)
Investigation		
Increased total WBC counts	01 (01.67 %)	00 (00.00 %)
Decreased haemoglobin	03 (05.00 %)	07 (11.29 %)
Total	08 (13.33 %)	11 (17.74 %)

4.1.2.2.4 Protocol Deviations

Study No. 16-VIN-0236		
Type	Subject #s (Test)	Subject #s (Ref.)
Sampling Deviation	Period 01	(b) (6)
	Period 02	
Other deviations		
For subject (b) (6) pre-patch application blood sample was not collected within one hour prior to patch application. Pre-patch application blood sample was collected at 08:07 hours and patch application was done at 09:18 in period 01.	Period 01	
Clinical Research Physician did not follow ±30 minutes criteria for patch adhesion performance scoring at 24.00 hours' time points on 21 Feb 2018 for subject (b) (6). Schedule time for patch adhesion performance scoring for subject (b) (6) was 08:46 hours instead activity was performed by CRP at 09:19 hours on 21 Feb 2018.	Period 01	
For 14 subjects of group 03 of the study, the duration of the clinical part of this study exceeded upto approximately 41 days instead 40 days.	Not applicable	
Total 64 subjects were enrolled in to the study instead of 66 subjects.	Period 01	
For subject no. (b) (6) study safety assessment was performed on 16 Apr 2018. In post study safety assessment Hematology report, subject's Hemoglobin was observed out of acceptable range, hence adverse event was reported for the same. Subject was advised to report to facility. Then subject was contacted telephonically repeatedly for follow up, but she did not report to facility till date, hence considered as lost to follow up.	End study	
For subject no. (b) (6) post study safety assessment was performed on 27 Apr 2018. In post study safety assessment Hematology report, subject's Hemoglobin was observed out of acceptable range, hence adverse event was reported for the same. Subject was advised to report to facility. Then subject was contacted	End study	

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

telephonically repeatedly for follow up, but she did not report to facility till date, hence considered as lost to follow up.		
For subject no. (b) (6) group 02 and subject no. (b) (6) group 03 post study safety assessment were performed on 16 Apr 2018 and 27 Apr 2018 respectively. In post study safety assessment Hematology report, both subject's Hemoglobin was observed out of acceptable range, hence adverse event was reported for the same. Subjects were advised to report to facility. Then subjects were contacted telephonically repeatedly for follow up, but both subjects did not report to facility till date, hence considered as lost to follow up.	End study	--

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Reassays and Reporting of Final Concentrations

Bioanalytical Method Validation for Ethinyl Estradiol - Study # 16-VIN-0236 (170273ARKC) (Fasting)

Information Requested	Data
Bioanalytical method validation report location	Not Applicable
Analyte	Ethinyl estradiol
Internal standard (IS)	Ethinyl estradiol-d ₄
Method description	This method involves the extraction of ethinyl estradiol and the internal standard ethinyl estradiol-d ₄ from human EDTA K ₂ plasma using a liquid-liquid extraction and derivatization procedure and LC-MS/MS determination according to method SOP (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.600 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	1.00 Original validation report
Average recovery of drug (%)	103.53, 99.69 and 98.31 Original validation report
Average recovery of IS (%)	109.73 Original validation report

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

Information Requested	Data
Standard curve concentrations (pg/mL)	1.00, 2.00, 20.00, 40.00, 80.00, 160.00, 320.00, 400.00 Original validation report
QC concentrations (pg/mL)	LLQC: 1.00, QC1: 3.00, QC2: 100.00, QC3: 150.00 Partial validation 1
QC Intraday precision range (%)	0.87 to 6.03 Partial validation 1
QC Intraday accuracy range (%bias)	-7.17 to -3.07 Partial validation 1
QC Interday precision range (%)	1.54 to 9.84 Original validation report
QC Interday accuracy range (%bias)	1.85 to 8.90 Original validation report
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24h10min at room temperature Original validation report
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte: 325 days at -20°C Internal standard: 367 days at -20°C Original validation report
Processed stability (hrs) (equivalent to post-preparative stability)	71h50min at 4°C Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20°C Original validation report 4 cycles at -20°C (fortified with 17-desacetylnorgestimate) Interference report
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	427 days at -20°C Original validation report 95 days at -20°C (fortified with 17-desacetylnorgestimate) Interference report
Dilution integrity	DQC diluted 1/20: 2000.00 pg/mL %CV: 0.59 %Bias: 1.41 Original validation report
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard. Original validation report

**Bioanalytical Method Validation for 17-Desacetylnorgestimate - Study # 16-VIN-0236
(170273ARKD) (Fasting)**

Information Requested	Data
Bioanalytical method validation report location	Not Applicable
Analyte	17-desacetylnorgestimate
Internal standard (IS)	17-desacetylnorgestimate-d ₆
Method description	This method involves the extraction of 17-desacetylnorgestimate and the internal standard 17-desacetylnorgestimate-d ₆ from human EDTA K ₂ plasma using an automated liquid-liquid extraction procedure and LC-MS/MS determination according to method SOP (b) (4) (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.200 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	50.00 Original validation report
Average recovery of drug (%)	95.13, 93.55 and 91.59 Original validation report
Average recovery of IS (%)	103.42 Original validation report
Standard curve concentrations (pg/mL)	50.00, 100.00, 200.00, 300.00, 600.00, 1800.00, 2400.00, 3000.00 Original validation report
QC concentrations (pg/mL)	LLQC: 50.00, QC1: 150.00, QC2: 1500.00, QC3: 2250.00 Original validation report
QC Intraday precision range (%)	1.00 to 4.95 Original validation report
QC Intraday accuracy range (%bias)	-6.05 to 0.77 Original validation report
QC Interday precision range (%)	4.58 to 5.64 Original validation report
QC Interday accuracy range (%bias)	-3.39 to 3.32 Original validation report
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24h00min at room temperature
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte: 254 days at -20°C Internal standard: 159 days at -20°C Original validation report
Processed stability (hrs) (equivalent to post-preparative stability)	95h52min at room temperature Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20°C Original validation report

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

Information Requested	Data
	4 cycles at -20°C (fortified with ethinyl estradiol) Interference report (revision 02)
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	909 days at -20°C Original validation report 909 days at -20°C Interference report (revision 02)
Dilution integrity	DQC diluted 1/20: 30000.00 pg/mL %CV: 1.56 %Bias: -4.85 Original validation report
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard. Original validation report

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses for Ethinyl estradiol - Study # 16-VIN-0236 (170273ARKC) (Fasting)

Bioequivalence Study No. 170273ARKC								
Ethinyl Estradiol								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	1.00	2.00	4.00	20.00	40.00	80.00	160.00	200.00
Interday Precision (%CV)	3.62	6.31	1.96	1.51	1.43	1.38	1.44	1.45
Interday Accuracy (%bias)	-0.40	2.70	-2.15	-2.53	2.21	3.55	-0.58	-2.04
Linearity	0.9974 to 0.9994							
Linearity Range (pg/mL)	1.00 to 200.00							
Sensitivity/LOQ (pg/mL)	1.00							

Bioequivalence Study No. 170273ARKC				
Ethinyl Estradiol				
Parameter	Quality Control Samples			
Concentration (pg/mL)	3.00	10.00	100.00	150.00
Interday Precision (%CV)	4.43	2.91	2.45	3.26
Interday Accuracy (%bias)	-4.63	-4.35	-2.51	-2.87

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses for 17-desacetylnorgestimate- Study # 16-VIN-0236 (170273ARKD) (Fasting)

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

Bioequivalence Study No. 170273ARKD									
17-Desacetylnorgestimate									
Parameter		Standard Curve Samples							
Concentration (pg/mL)		50.00	100.00	200.00	300.00	600.00	1800.00	2400.00	3000.00
Interday (%CV)	Precision	3.19	3.00	2.30	3.03	2.43	2.39	2.39	2.71
Interday (%bias)	Accuracy	0.35	-0.31	-1.40	0.96	-0.26	0.42	-0.26	0.49
Linearity		0.9993 to 0.9978							
Linearity (pg/mL)	Range	50.00 to 3000.00							
Sensitivity/LOQ (pg/mL)		50.00							

Bioequivalence Study No. 170273ARKD									
17-Desacetylnorgestimate									
Parameter		Quality Control Samples							
Concentration (pg/mL)		150.00		250.00		1500.00		2250.00	
Interday (%CV)	Precision	3.91		3.35		2.71		2.50	
Interday (%bias)	Accuracy	1.22		-0.51		0.83		-0.08	

4.1.2.3.3 Reanalysis of Study Samples

Study No. 170273ARKC									
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis				
	Actual number		% of total assays		Actual number		% of total assays		
	T	R	T	R	T	R	T	R	
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00	
Unacceptable internal standard response	0	2	0.00	0.08	0	2	0.00	0.08	
Sample reanalyzed to obtain confirming value	1	0	0.04	0.00	1	0	0.04	0.00	
Total	1	2	0.04	0.08	1	2	0.04	0.08	

¹If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Study No. 170273ARKD								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00
Total	0	0	0.00	0.00	0	0	0.00	0.00

¹If no repeats were performed for pharmacokinetic reasons, insert "0.0."

4.1.2.4 Formulation Data

Formula for Batch # PW-ST-17042A			
Sr. #	Ingredients	% w/w	
Patch size-14.4 cm²			
1	Norelgestromin, USP	(b) (4)	
2	Ethinyl Estradiol, USP (Micronized)		
3	(b) (4)		
6	Crospovidone NF, (b) (4) (b) (4)		
7	Oleyl Alcohol NF (b) (4) (b) (4)		
8	Dipropylene Glycol		
9	Polybutene (b) (4) (b) (4)		
Total			100.0

4.1.2.5 Pharmacokinetic Results

4.1.2.5.1 Geometric Means and 90% Confidence Intervals - Firm Calculated

Reference Scaled Average Bioequivalence Approach Used	☐ Yes	☒ No
Norelgestromin (No of subjects completed= 59)		
Dose (150 mcg/day Transdermal System)		
Least Squares Geometric Means Ratio and 90% Confidence Intervals		
Fasted Bioequivalence Study (Study No. 16-VIN-0236)		

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

Parameters	Test	N*	RLD	N	Ratio of Geometric Means	90% C.I.
AUC _{0-t} (hr*pg/mL)	197143	59	171789	59	114.76	110.28 – 119.42
AUC _{0-∞} (hr*pg/mL)	209689	59	182844	59	114.68	110.29 – 119.24
C _{max} (pg/mL)	1240	59	1084	59	114.45	109.65 – 119.47
Ethinyl Estradiol (No of subjects completed= 59) Dose (35 mcg/day Transdermal System) Least Squares Geometric Means Ratio and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. 16-VIN-0236)						
Parameters	Test	N	RLD	N	Ratio of Geometric Means	90% C.I.
AUC _{0-t} (hr*pg/mL)	8000	59	6700	59	119.40	113.56 – 125.55
AUC _{0-∞} (hr*pg/mL)	8088	59	6780	58	119.29	113.41 – 125.49
C _{max} (pg/mL)	56.9	59	47.1	59	120.66	114.59 – 127.06

Was the Fasting bioequivalence study acceptable? Not acceptable.

Assessor's Comments

- This is a failed pivotal fasting BE study conducted in 59 subjects (completed) dosed in 3 groups. The study design is the same as the passed pivotal BE study (No. ESTN/2018/1607). The 90% CIs for Ln AUC_t, LnAUC_i and LnC_{max} met the BE criteria for NGMN. However, the 90% CIs for all these parameters failed to meet BE criteria for EE. The T/R ratios for all the parameters for EE are very high, closer to 1.20.
- The test formulation used in this study (batch # PW-ST-17042A) is different from the final test formulation (batch #PW-ST-18020A) used in the passed pivotal study. The RS Batch (No. 3086481) is also different from that used in the passed pivotal study (Batch No. 3098718). Please see the comparison of test formulations in the two pivotal studies below. The firm submitted %w/w for all the ingredients and did not submit the actual quantities in mg for the formulation composition. To further investigate this failed pivotal study, the firm will be asked to provide full study report and composition of test formulation, including the quantity in mg/patch for each active and inactive ingredient.

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (FAILED)

Table 42. Formula for Batch # PW-ST-17042A		PW-ST-18020A	
Sr. #	Ingredients	(b) (4)	
		% w/w Patch size 12.5 cm ²	
1	Norelgestromin, USP	(b) (4)	
2	Ethinyl Estradiol, USP (Micronized)	(b) (4)	
	(b) (4)	(b) (4)	
6	Crospovidone NF (b) (4)	(b) (4)	
7	Oleyl Alcohol NF (b) (4) (b) (4)	(b) (4)	
8	Dipropylene Glycol	(b) (4)	
9	Polybutene (b) (4)	(b) (4)	
Total		100.0	100.0

- After the failure of the current pivotal BE study (No. 16-VIN-0236) due to 90% CIs not meeting the upper limit of BE acceptance criteria for EE, the firm reformulated the test formulation with a (b) (4) (b) (4) in the final test formulation. (b) (4)

(b) (4)

4.1.3 Single-dose Failed Fasting Bioequivalence Study

4.1.3.1 Study Design

4.1.3.1.1 Study Information

Study Number	16-VIN-0235			
Study Title	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Two-Period, Single-Application, Crossover Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals and Xulane™ (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day distributed by Mylan Pharmaceuticals Inc., Morgantown, WV 26505 in Healthy, Adult, Human Female Subjects under fasting condition			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Submission Location	Not Applicable			
Study Report	Not Applicable			
Validation Report	Not Applicable			
Bioanalytical Report	Not Applicable			
Clinical Site (Name, Address, Phone #, Fax #)	Veeda Clinical Research Pvt. Ltd. Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India Tel. No.: +91-79-30013000; Fax No.: +91-79-30013010			
Principal Clinical Investigator (Name, Email)	Dr. Hiren Prajapati, MD (Pharmacology) hiren.prajapati@veedacr.com			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Principal Analytical Investigator (Name, Email)				
Sample Storage : (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20° C to -80° C)	Ethinyl estradiol (160396APVS): a) 60 days (19-JAN-2017 to 20-MAR-2017) b) -20°C 17-desacetylnorgestimate (160396APVT): a) 56 days (19-JAN-2017 to 16-MAR-2017) b) -20°C			
Long-Term Storage Stability (LTSS) Coverage (no. days @ °C) temp	Ethinyl estradiol (160396APVS): 181 days at -20°C 95 days at -20°C (fortified with 17-desacetylnorgestimate)			

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

	17-desacetylnorgestimate (160396APVT): 909 days at -20°C 909 days at -20°C (fortified with ethinyl estradiol)
LTSS Data Location	Not Applicable

4.1.3.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day	Xulane® (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day
Manufacturer	Anneal Pharmaceuticals LLC	Distributed by Mylan Pharmaceuticals Inc. Morgantown, WV26505 U.S.A.
Batch No./Lot No.	B10103-072 (Batch No.)	615264 (Lot No.)
Manufacturing Date	04 Aug 2016	Not applicable
Expiration Date	Not applicable	Dec 2017
Strength	150/35 mcg per day	150/35 mcg per day
Dosage Form	Transdermal Patch	Transdermal Patch
Bio-batch Size	(b) (4) Feet	Not Applicable
Production Batch Size	Not Applicable	Not Applicable
Potency	Norelgestromin - 100.5 %	Norelgestromin - 99.9 %
	Ethinyl Estradiol - 101.5 %	Ethinyl Estradiol - 98.4 %
Content Uniformity (mean, %CV) - Ethinyl Estradiol & Norelgestromin	Not Applicable	Not Applicable
Dose Administered	150/35 mcg per day for 07 days	150/35 mcg per day for 07 days
Route of Administration	Topical	Topical

4.1.3.2 Clinical Results

4.1.3.2.1 Demographic Profile of Subjects

Study No. 16-VIN-0235

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

		Treatment Groups	
		Test Product (T) N =34	Reference Product (R) N =34
Age (years)	Mean ± SD	30.26 ± 3.26	30.26 ± 3.26
	Range	22 – 34	22 – 34
Age Groups	< 18	00 (00.00%)	00 (00.00%)
	18 – 40	34 (100.00%)	34 (100.00%)
	41 – 64	00 (00.00%)	00 (00.00%)
	65 – 75	00(00.00%)	00(00.00%)
	> 75	00(00.00%)	00(00.00%)
Sex	Male	00 (00.00%)	00 (00.00%)
	Female	34 (100.00%)	34 (100.00%)
Race	Asian	34 (100.00%)	34 (100.00%)
	Black	00(00.00%)	00(00.00%)
	Caucasian	00(00.00%)	00(00.00%)
	Hispanic	00(00.00%)	00(00.00%)
	Other	00(00.00%)	00(00.00%)
BMI (Kg/m ²)	Mean ± SD	25.03 ± 2.51	25.03 ± 2.51
	Range	20.14 – 29.90	20.14 – 29.90
Height (cm)	Mean ± SD	152.78 ± 5.90	152.78 ± 5.90
	Range	140.00 – 168.00	140.00 – 168.00
Weight (Kg)	Mean ± SD	58.46 ± 7.16	58.46 ± 7.16
	Range	50.50 – 78.00	50.50 – 78.00

4.1.3.2.2 Dropout Information

Study No. 16-VIN-0235				
Subject No	Reason for dropout/replacement	Period	Replaced	Replaced with
(b) (6)	Adverse event Date & Time : 17 Feb 2017; 23:40 Last treatment: R	Period 02	No	NA
	Subject has been withdrawn due to protocol violation. Date & Time : 26 Jan 2017; 11:30 Last treatment: R	Period 01	No	NA

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Study No. 16-VIN-0235				
Subject No	Reason for dropout/replacement	Period	Replaced	Replaced with
(b) (6)	Subject withdrawn consent Date & Time : 19 Jan 2017; 08:30 Last treatment: NA	Period 01	Yes	(b) (6)
(b) (6)	Subject withdrawn consent Date & Time : 19 Jan 2017; 08:31 Last treatment: NA	Period 01	Yes	(b) (6)

4.1.3.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups		
	Fast Bioequivalence Study Study No. 16-VIN-0235		
	Test Product (T)	Reference Product (R)	Not related with investigational product
Gastrointestinal System			
Vomiting	-	01 (2.78%)	-
Others			
Decreased haemoglobin	04 (11.76%)	03(8.33%)	-
Decreased platelet count	01 (02.94%)	-	-
Increased B-HCG	-	-	01
Total	05 (14.71%)	04 (11.11%)	01 (2.78%)

Note: 34 subjects exposed with test (T) products and 36 subjects exposed with Reference (R) product.

4.1.3.2.4 Protocol Deviations

Study No. 16-VIN-0235			
Type	Subject #s (Test:T)		Subject #s (Reference: R)
Sampling Deviation	Period 01	(b) (6)	
	Period 02	(b) (6)	
Other deviations			

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Patch site examination was not followed as per protocol for below mentioned subjects.					Period 01	(b) (6)
Period	Subject number	Time point (hr)	Schedule time	Actual time	Period 02	
01	(b) (6)	144	09:08	10:03		
02	(b) (6)	144	09:16	10:06		
02	(b) (6)	144	09:18	10:07		
02	(b) (6)	168	09:18	11:04		
Adhesion performance scoring was not followed for below mentioned subjects					Period 01	
Period	Subject number	Time point (hr)	Schedule time	Actual time	Period 02	
01	(b) (6)	144	09:08	10:03		
02	(b) (6)	120	09:18	09:50		
02	(b) (6)	144	09:18	10:00		
02	(b) (6)	120	09:20	09:53		
02	(b) (6)	120	09:22	09:53		
After completion of each clinical study period, the plasma samples were transferred from the clinical research facility to the bioanalytical facility of in (b) (4) and stored at below -15 °C until analysis. While transferring the samples, adequate measures were taken for maintaining the temperature and integrity of samples.					--	
For subject no.03, post study safety assessment was performed on 28 Feb 2017. In past study safety assessment haemogram report, subject's haemoglobin was observed out of range, hence adverse event was generated for the same. Subject was contacted telephonically repeatedly for follow-up, but she did not report to facility till date, hence considered as lost to follow-up.					--	

4.1.3.3 Bioanalytical Results

4.1.3.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Sample Reassays and Reporting of Final Concentrations

Bioanalytical Method Validation for Ethinyl Estradiol - Study # 16-VIN-0235 (160396APVS) (Fasting)

Information Requested	Data
Bioanalytical method validation report location	Not Applicable
Analyte	Ethinyl estradiol
Internal standard (IS)	Ethinyl estradiol-d ₄
Method description	This method involves the extraction of ethinyl estradiol and the internal standard ethinyl estradiol-d ₄ from human EDTA K ₂ plasma using a liquid-liquid extraction and derivatization procedure and LC-MS/MS determination according to method SOP (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.600 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	1.00 Original validation report (revision 01)
Average recovery of drug (%)	106.23, 102.22 and 94.73 Original validation report (revision 01)
Average recovery of IS (%)	106.59 Original validation report (revision 01)
Standard curve concentrations (pg/mL)	1.00, 2.00, 4.00, 20.00, 40.00, 80.00, 160.00 and 200.00 Original validation report (revision 01)
QC concentrations (pg/mL)	LLQC: 1.00, QC1: 3.00, QC2: 100.00, QC3: 150.00 Original validation report (revision 01)
QC Intraday precision range (%)	0.78 to 6.34 Original validation report (revision 01)
QC Intraday accuracy range (%bias)	-8.83 to -1.27 Original validation report (revision 01)
QC Interday precision range (%)	0.92 to 12.96 Original validation report (revision 01)
QC Interday accuracy range (%bias)	-4.06 to -0.33 Original validation report (revision 01)
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24 hours and 14 minutes at room temperature Original validation report (revision 01)
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analytes: 325 days at -20°C IS: 367 days at -20°C Original validation report (revision 01)
Processed stability (hrs) (equivalent to post-preparative stability)	71 hours and 45 minutes at 4°C followed by 48h45min at room temperature Original validation report (revision 01)
Freeze-thaw stability (cycles)	4 cycles at -20°C (Fortified with 17-Desacetylnorgestimate) Interference report

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Information Requested	Data
	4 cycles at -20°C Original validation report (revision 01)
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	95 days at -20°C (Fortified with 17-Desacetylnorgestimate) Interference report 181 days at -20°C Original validation report (revision 01)
Dilution integrity	DQC diluted 1/20: 2012.00 pg/mL %CV : 2.92 %Bias: -2.99 Original validation report (revision 01)
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard Original validation report (revision 01)

Bioanalytical Method Validation for 17-Desacetylnorgestimate - Study # 16-VIN-0235 (160396APVT) (Fasting)

Information Requested	Data
Bioanalytical method validation report location	Not applicable
Analyte	17-desacetylnorgestimate
Internal standard (IS)	17-desacetylnorgestimate-d ₆
Method description	This method involves the extraction of 17-desacetylnorgestimate and the internal standard 17-desacetylnorgestimate-d ₆ from human EDTA K ₂ plasma using an automated liquid-liquid extraction with methyl tert-butyl ether procedure and LC-MS/MS determination according to method SOP (b) (4). Samples were kept frozen at -20°C prior to analysis and 0.200 mL of matrix was used for analysis.
Limit of quantitation (pg/mL)	50.00 Original validation report (Revision 02)
Average recovery of drug (%)	95.13, 93.55 and 91.59 Original validation report (Revision 02)
Average recovery of IS (%)	103.42 Original validation report (Revision 02)
Standard curve concentrations (pg/mL)	50.00, 100.00, 200.00, 300.00, 600.00, 1800.00, 2400.00 and 3000.00 Original validation report (Revision 02)

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Information Requested	Data
QC concentrations (pg/mL)	LLQC: 50.00, QC1: 150.00, QC2: 1500.00, QC3: 2250.00 Original validation report (Revision 02)
QC Intraday precision range (%)	1.00 to 4.95 Original validation report (Revision 02)
QC Intraday accuracy range (%bias)	-6.05 to 0.77 Original validation report (Revision 02)
QC Interday precision range (%)	4.58 to 5.64 Original validation report (Revision 02)
QC Interday accuracy range (%bias)	-3.39 to 3.32 Original validation report (Revision 02)
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24 hours and 00 minutes at room temperature Original validation report (Revision 02)
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Analyte: 254 days at -20°C IS: 159 days at -20°C Original validation report (Revision 02)
Processed stability (hrs) (equivalent to post-preparative stability)	95 hours and 52 minutes at room temperature Original validation report
Freeze-thaw stability (cycles)	4 cycles at -20°C (Fortified with ethinyl estradiol) Interference report (Revision 02) 4 cycles at -20°C Original validation report (Revision 02)
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	909 days at -20°C (Fortified with ethinyl estradiol) Interference report (Revision 02) 909 days at -20°C Original validation report (Revision 02)
Dilution integrity	DQC diluted 1/20: 30000.00 pg/mL %CV : 1.56 %Bias: -4.85 Original validation report (Revision 02)
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard Original validation report (Revision 02)

4.1.3.3.2 Sample Analysis Calibration and Quality Control

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses for Ethinyl estradiol - Study # 16-VIN-0235 (160396APVS) (Fasting)

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Bioequivalence Study No. 160396APVS								
Ethinyl Estradiol								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	1.00	2.00	4.00	20.00	40.00	80.00	160.00	200.00
Interday Precision (%CV)	6.00	4.50	4.18	3.28	3.45	3.90	3.21	2.42
Interday Accuracy (%bias)	0.00	0.00	1.75	2.15	0.13	-0.68	-1.62	-1.16
Linearity	0.9930 to 0.9996							
Linearity Range (pg/mL)	1.00 to 200.00							
Sensitivity/LOQ (pg/mL)	1.00							
Bioequivalence Study No. 160396APVS								
Ethinyl Estradiol								
Parameter	Quality Control Samples							
Concentration (pg/mL)	3.00		10.00		100.00		150.00	
Interday Precision (%CV)	4.91		3.97		5.08		3.60	
Interday Accuracy (%bias)	-5.00		-4.20		-4.57		-4.44	

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses for 17-desacetylnorgestimate- Study # 16-VIN-0235 (160396APVT) (Fasting)

Bioequivalence Study No. 160396APVT								
17-Desacetylnorgestimate								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	50.00	100.00	200.00	300.00	600.00	1800.00	2400.00	3000.00
Interday Precision (%CV)	4.91	4.03	3.75	3.58	2.66	2.69	3.19	3.10
Interday Accuracy (%bias)	-0.24	0.26	1.38	-1.22	-0.63	-0.23	0.98	-0.32
Linearity	0.9955 to 0.9988							
Linearity Range (pg/mL)	50.00 to 3000.00							
Sensitivity/LOQ (pg/mL)	50.00							
Bioequivalence Study No. 160396APVT								
17-Desacetylnorgestimate								
Parameter	Quality Control Samples							
Concentration (pg/mL)	150.00		250.00		1500.00		2250.00	
Interday Precision (%CV)	5.71		5.18		7.63		4.35	
Interday Accuracy (%bias)	1.96		1.91		3.67		3.24	

4.1.3.3.3 Reanalysis of Study Samples

Reanalysis of Study Samples for Ethinyl Estradiol - Study # 16-VIN-0235 (160396APVS) (Fasting)

Study No. 160396APVS								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	0	1	0.00	0.07	0	1	0.00	0.07
Loss of sample during processing	1	1	0.07	0.07	1	1	0.07	0.07
The internal standard response is lower than 5% of the mean internal standard responses	1	1	0.07	0.07	1	1	0.07	0.07
Sample reanalyzed to obtain confirming value	1	0	0.07	0.00	0	0	0.00	0.00
Total	3	3	0.20	0.20	2	3	0.13	0.20

¹If no repeats were performed for pharmacokinetic reasons, insert "0.0."

Reanalysis of Study Samples for 17-desacetylnorgestimate- Study # 16-VIN-0235 (160396APVT) (Fasting)

Study No. 160396APVT								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic ¹	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable internal standard response	1	0	0.07	0.00	1	0	0.07	0.00
Total	1	0	0.07	0.00	1	0	0.07	0.00

¹If no repeats were performed for pharmacokinetic reasons, insert "0.0."

4.1.3.4 Formulation Data

Formula for Batch # 10103-72			
Sr. #	Ingredients	% w/w	
1	Norelgestromin, USP	(b) (4)	
2	Ethinyl Estradiol, USP (Micronized)		
(b) (4)			
6	Crospovidone NF, (b) (4)		
7	Oleyl Alcohol NF (b) (4)		
8	Dipropylene Glycol		
9	Oppanol (b) (4)		
Total			100.0

4.1.3.5 Pharmacokinetic Results

4.1.3.5.1 Geometric Means and 90% Confidence Intervals - Firm Calculated

Reference Scaled Average Bioequivalence Approach Used	☐ Yes	☒ No				
Norelgestromin (No of subjects completed=34) Dose (150 mcg/day Transdermal System) Least Squares Geometric Means Ratio and 90% Confidence Intervals						
Fasted Bioequivalence Study (Study No. 16-VIN-0235)						
Parameters	Test	N*	RLD	N	Ratio of Geometric Means	90% C.I.
AUC _{0-t} (hr*pg/mL)	164517.332	34	161627.246	34	101.79	96.70% - 107.14%
AUC _{0-∞} (hr*pg/mL)	172461.485	34	169602.988	34	101.69	96.65% - 106.98%

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

C _{max} (pg/mL)	1088.418	34	1063.746	34	102.32	97.00% - 107.93%
Ethinyl Estradiol (No of subjects completed= 33)						
Dose (35 mcg/day Transdermal System)						
Least Squares Geometric Means Ratio and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. 16-VIN-0235)						
Parameters	Test	N**	RLD	N	Ratio of Geometric Means	90% C.I.
AUC _{0-t} (hr*pg/mL)	8394.567	33	6716.411	33	124.99	117.50% - 132.95%
AUC _{0-∞} (hr*pg/mL)	8487.611	33	6757.857	32	125.60	117.90% - 133.80%
C _{max} (pg/mL)	59.114	33	47.566	33	124.28	116.33% - 132.77%

Was the fasting bioequivalence study acceptable? Not acceptable.

Assessor's Comments

- This is a pilot fasting BE study (34 subjects completed for NGMN and 33 subjects completed for EE). The study design (single-dose, two-way cross over) is same as that in pivotal BE studies (Nos. 16-VIN-0236 and ESTN/2018/1607). The 90% CIs for Ln AUC_t, AUC_i and C_{max} met the BE criteria for NGMN. However, all these parameters failed to meet BE criteria for EE. The test formulation (batch No. B10103-072) used in this study is different from the test formulation used in the passed pivotal study (batch No. PW-ST-18020A) and failed pivotal study (batch No. PW-ST-17042A). For EE, the T/R ratios for AUC_t and C_{max} are close to 125.00%, and the T/R ratio for AUC_i (125.60%) exceeds 125.00%.
- After the failure of the pilot BE study (No. 16-VIN-0235), due to 90% CIs not meeting the BE acceptance criteria for EE, the firm modified the formulation with (b) (4) (b) (4) was used in test Batch # PW-ST-17042A, instead of (b) (4) used in Batch #10103-72. (b) (4) (b) (4) Amneal's Norelgestromin and Ethinyl Estradiol patch and to match (b) (4) XULANE®. The differences between Batch# 10103-072 (pilot) and the reformulated Batch# PW-ST 17042A used for the failed pivotal PK study are presented below. The firm will be asked to provide the full study report and composition of test formulation, including the quantity in mg/patch for each active and inactive ingredient.

ANDA 213950
Single-Dose Fasting Bioequivalence Study Review (PILOT)

Table 41. Formula for Batch # 10103-72			PW-ST-17042A
Sr. #	Ingredients	% w/w	% w/w
			(b) (4)
1	Norelgestromin, USP		(b) (4)
2	Ethinyl Estradiol, USP (Micronized)		(b) (4)
			(b) (4)
6	Crospovidone NF, (b) (4)		(b) (4)
7	Oleyl Alcohol NF (b) (4) (b) (4)		(b) (4)
8	Dipropylene Glycol		(b) (4)
9	Polybutene (b) (4)		(b) (4)
10	Oppanol (b) (4)		(b) (4)
Total		100.0	100.0

4.2 Formulation Data

4.2.1 Test Formulation

Ingredients	Quantity in mg/patch	Quantity in %w/w	Function
Ethinyl Estradiol, USP (Micronized)	0.289	(b) (4)	API
Norelgestromin, USP	3.15		API
Polyisobutylene/Polybutene Adhesive (b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
Crospovidone, NF (b) (4)			
Oleyl Alcohol, NF (b) (4)			
Dipropylene Glycol (b) (4)			
(b) (4)			
Total Weight of Adhesive Ingredients			
(b) (4)			

Ingredients	Quantity in mg/patch	Quantity in %w/w	Function
(b) (4)			

Ingredients	Size / Patch	Function
(b) (4) Pigmented Polyethylene and Polyester printed with Norelgestromin and Ethinyl Estradiol Transdermal System 150/35mcg per day)	12.5 cm ² (Equivalent to 57.75 mg/patch)	Backing Film
(b) (4) (polyethylene terephthalate film with silicone coating) (6 inch wide)	> 12.5 cm ² , oversized release liner	Release Liner
(b) (4)		

4.3 Dissolution Testing

Dissolution Data

Anneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18020A (Biobatch) vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day - Norelgestromin

Dissolution Conditions		Apparatus:	USP Type V (Paddle over Disk)													
		Speed of Rotation:	50 RPM													
		Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin													
		Volume:	900 mL													
		Temperature:	32°C ± 0.5°C													
Firm's Proposed Specifications		Time / % Release: 0.25 hour (15 min) / NMT (b)(4)%; 0.5 hour (30 min) / (b)(4)%; 1 hour / (b)(4)%; 2 hours / (b)(4)%; 4 hours / (b)(4)%; 8 hours / (b)(4)%; 12 hours / NLT (b)(4)%, 16 hours / NL (b)(4)%, 20 hours / NLT (b)(4)%, 24 hours / NLT (b)(4)%														
Dissolution Testing Site (Name, Address)		Anneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/15/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18020A Mfg. Date: 10/02/2018	150/35 mcg/day Transdermal System	12	Mean	8	16	27	41	61	86	96	98	98	98	Module 5.3.1.3
					Range	(b)(4)										
					%CV	10.5	3.1	2.5	2.5	3.9	2.6	1.4	1.2	0.9	0.7	
	05/16/19			12	Mean	6	13	25	41	58	78	89	96	99	100	

		Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System		Range	(b) (4)										
					%CV	14.0	8.7	7.7	6.1	4.9	5.3	4.2	2.4	1.8	1.4	

Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18021B vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day - **Norelgestromin**

Dissolution Conditions	Apparatus:	USP Type V (Paddle over Disk)														
	Speed of Rotation:	50 RPM														
	Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin														
	Volume:	900 mL														
	Temperature:	32°C ± 0.5°C														
Firm's Proposed Specifications	Time / % Release: 0.25 hour (15 min) / NMT (b)(4) ; 0.5 hour (30 min) / (b)(4) %; 1 hour / (b)(4) %; 2 hours / (b)(4) %; 4 hours / (b)(4) %; 8 hours / (b)(4) %; 12 hours / NLT (b)(4) , 16 hours / NLT (b)(4) , 20 hours / NLT (b)(4) % , 24 hours / NLT (b)(4)															
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/13/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18021B Mfg. Date: 10/18/2018	150/35 mcg/day Transdermal System	12	Mean	9	16	27	41	61	86	94	95	96	96	Module 5.3.1.3
					Range	(b)(4)										
					%CV	17.5	7.1	5.2	4.3	3.4	2.8	1.2	0.9	1.0	0.8	
	05/16/19	Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System	12	Mean	6	13	25	41	58	78	89	96	99	100	
					Range	(b)(4)										
					%CV	14.0	8.7	7.7	6.1	4.9	5.3	4.2	2.4	1.8	1.4	

Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18022B vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day - **Norelgestromin**

Dissolution Conditions	Apparatus:	USP Type V (Paddle over Disk)														
	Speed of Rotation:	50 RPM														
	Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin														
	Volume:	900 mL														
	Temperature:	32°C ± 0.5°C														
Firm's Proposed Specifications	Time / % Release: 0.25 hour (15 min) / NMT (b)(4)%; 0.5 hour (30 min) (b)(4)%; 1 hour / (b)(4)%; 2 hours / (b)(4) ; 4 hours / (b)(4) ; 8 hours / (b)(4)%; 12 hours / NLT (b)(4)%, 16 hours / NLT (b)(4) , 20 hours / NLT (b)(4)%, 24 hours / NLT (b)(4)%															
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/13/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18022B Mfg. Date: 10/26/2018	150/35 mcg/day Transdermal System	12	Mean	11	17	27	42	63	88	97	98	97	97	Module 5.3.1.3
					Range	(b)(4)										
					%CV	6.1	3.5	3.3	3.0	1.7	0.8	1.2	1.0	0.9	1.1	
	05/16/19	Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System	12	Mean	6	13	25	41	58	78	89	96	99	100	
					Range	(b)(4)										
					%CV	14.0	8.7	7.7	6.1	4.9	5.3	4.2	2.4	1.8	1.4	

Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18020A (Biobatch) vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day – Ethinyl Estradiol

Dissolution Conditions	Apparatus:	USP Type V (Paddle over Disk)														
	Speed of Rotation:	50 RPM														
	Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin														
	Volume:	900 mL														
	Temperature:	32°C ± 0.5°C														
Firm's Proposed Specifications	Time / % Release: 0.25 hour (15 min) / NM (b)(4) ; 0.5 hour (30 min) / (b)(4)%; 1 hour / (b)(4)%; 2 hours (b)(4)%; 4 hours / (b)(4)%; 8 hours / (b)(4)%; 12 hours / NLT (b)(4)/(4), 16 hours / NLT (b)(4)/(4), 20 hours / NL (b)(4)/(4), 24 hours / NLT (b)(4)/(4)%															
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/15/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18020A Mfg. Date: 10/02/2018	150/35 mcg/day Transdermal System	12	Mean	10	20	33	52	76	94	98	99	99	99	Module 5.3.1.3
					Range	(b)(4)										
					%CV	9.5	3.3	2.7	2.6	3.5	1.8	0.8	0.8	0.6	1.0	
	05/16/19	Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System	12	Mean	7	16	29	46	67	88	95	98	100	100	
					Range	(b)(4)										
					%CV	11.9	6.5	4.4	2.6	3.1	2.8	1.9	1.3	0.8	1.6	

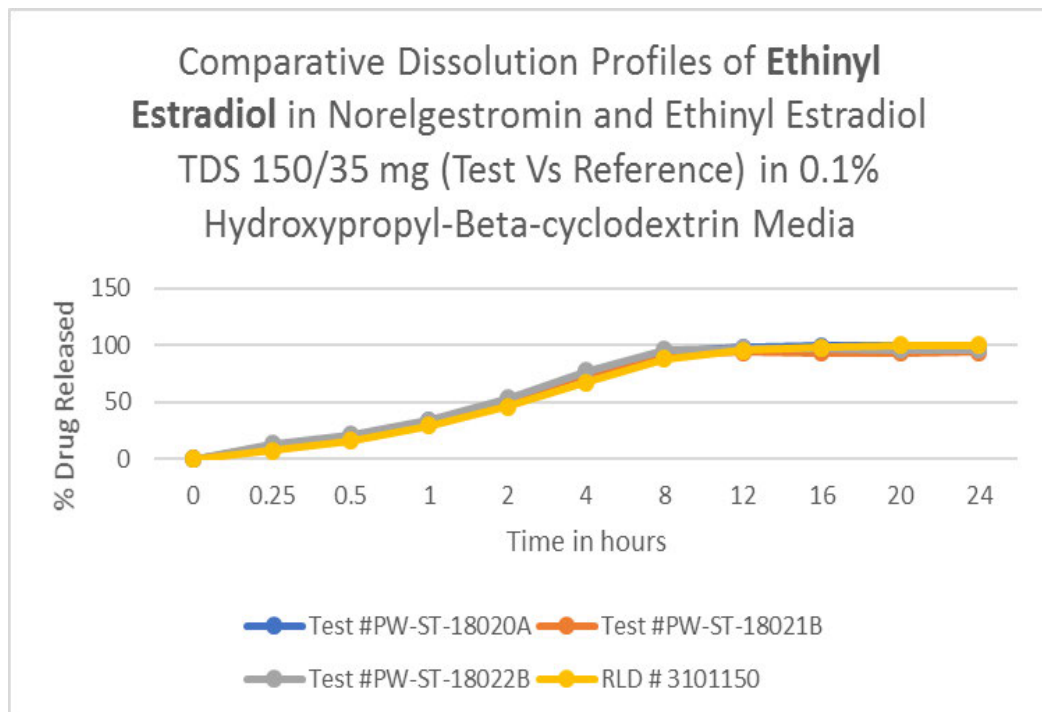
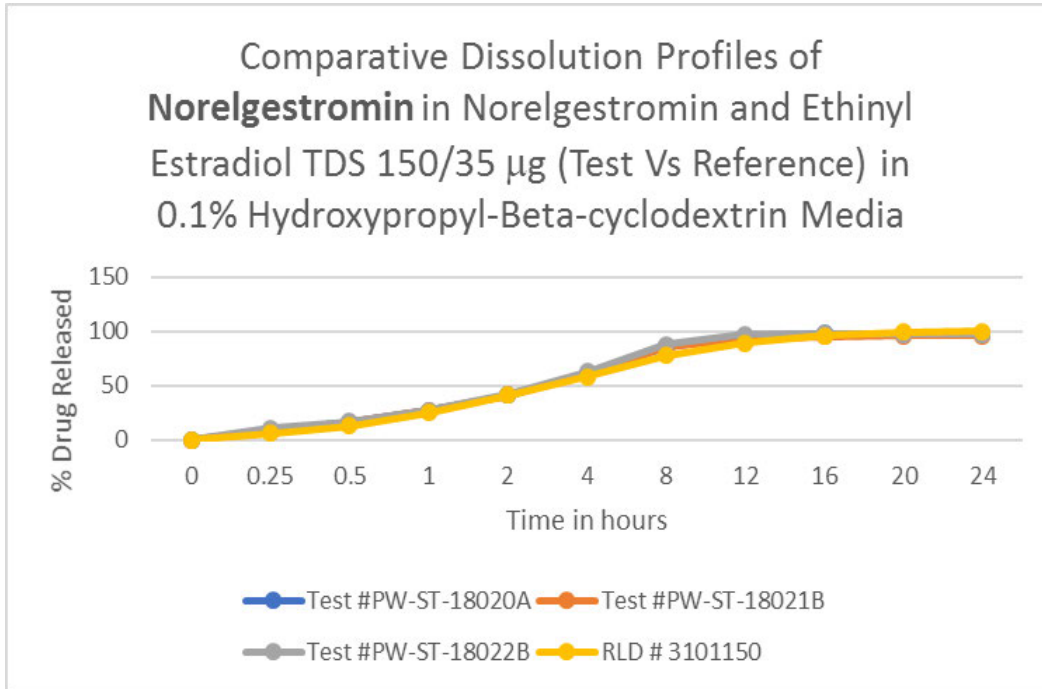
Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18021B vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day - **Ethinyl Estradiol**

Dissolution Conditions	Apparatus:	USP Type V (Paddle over Disk)														
	Speed of Rotation:	50 RPM														
	Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin														
	Volume:	900 mL														
	Temperature:	32°C ± 0.5°C														
Firm's Proposed Specifications	Time / % Release: 0.25 hour (15 min) / NM (b)(4); 0.5 hour (30 min) / (b)(4); 1 hour / (b)(4)%; 2 hours / (b)(4)%; 4 hours / (b)(4)%; 8 hours / (b)(4)%; 12 hours / NLT (b)(4)%, 16 hours / NL (b)(4)%, 20 hours / NLT (b)(4), 24 hours / NLT (b)(4)															
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/13/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18021B Mfg. Date: 10/18/2018	150/35 mcg/day Transdermal System	12	Mean	11	19	32	51	74	92	94	93	93	94	Module 5.3.1.3
					Range	(b)(4)										
					%CV	15.0	7.4	4.6	3.6	2.7	1.7	1.7	1.6	1.3	0.8	
	05/16/19	Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System	12	Mean	7	16	29	46	67	88	95	98	100	100	
					Range	(b)(4)										
					%CV	11.9	6.5	4.4	2.6	3.1	2.8	1.9	1.3	0.8	1.6	

Amneal's Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day - Lot # PW-ST-18022B vs Reference Product Xulane® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 mcg/day - **Ethinyl Estradiol**

Dissolution Conditions	Apparatus:	USP Type V (Paddle over Disk)														
	Speed of Rotation:	50 RPM														
	Medium:	0.1% Hydroxypropyl-Beta-cyclodextrin														
	Volume:	900 mL														
	Temperature:	32°C ± 0.5°C														
Firm's Proposed Specifications	Time / % Release: 0.25 hour (15 min) / NMT ^{(b) (4)} ; 0.5 hour (30 min) / ^{(b) (4)} %; 1 hour / ^{(b) (4)} %; 2 hours / ^{(b) (4)} %; 4 hours / ^{(b) (4)} %; 8 hours / ^{(b) (4)} %; 12 hours / NLT ^{(b) (4)} %, 16 hours / NLT ^{(b) (4)} %, 20 hours / NLT ^{(b) (4)} %, 24 hours / NLT ^{(b) (4)}															
Dissolution Testing Site (Name, Address)	Amneal Pharmaceuticals LLC 1 New England Avenue, Piscataway, NJ 08854															
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)										Study Report Location
						0.25 hr.	0.5 hr.	01 hr.	02 hrs	04 hrs	08 hrs	12 hrs	16 hrs	20 hrs	24 hrs	
PWY-19-MIS-032	05/13/19	Norelgestromin and Ethinyl Estradiol Batch # PW-ST-18022B Mfg. Date: 10/26/2018	150/35 mcg/day Transdermal System	12	Mean	13	21	34	53	77	96	97	97	96	96	Module 5.3.1.3
					Range	^{(b) (4)}										
					%CV	3.9	2.8	3.4	2.8	1.2	0.5	0.7	1.1	0.9	1.0	
	05/16/19	Xulane® (Norelgestromin and Ethinyl Estradiol) Batch # 3101150 Exp. Date: 10/2020	150/35 mcg/day Transdermal System	12	Mean	7	16	29	46	67	88	95	98	100	100	
					Range	^{(b) (4)}										
					%CV	11.9	6.5	4.4	2.6	3.1	2.8	1.9	1.3	0.8	1.6	

Dissolution Profiles



F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	No waiver request submitted in the current submission

Assessor Comments:

- The firm conducted dissolution testing using FDA recommended method⁴⁸ as shown in the following table.

USP Apparatus	Modified USP Type V (Paddle-over-disk)
Rotational speed	50 rpm
Medium	0.1% Hydroxypropyl-beta-cyclodextrin at 32 C± 0.5°C
Volume	900 mL
Sampling times	0.25, 0.5, 1, 2, 4, 8, 12, 16, 20 and 24 hours

- The Quality Control (QC) dissolution data will be reviewed separately by the Division of Biopharmaceutics at the Office of New Drug Products (ONDP) in the Office of Pharmaceutical Quality (OPQ) for establishing the batch releasing specifications. The QC dissolution testing is and is inadequate per preliminary assessment pending the acceptance of FDA recommended dissolution acceptance criteria for the drug product.⁴⁹ There is no waiver request submitted in the current application.

4.4 Attachments

4.4.1 ANDA 213950 Phoenix project file



ANDA213950 pAUC
and SSS Dev 042020

4.4.2 ANDA 213950 DABERS files

EE files

⁴⁸<https://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>

⁴⁹ GDRP, ANDA-213950-ORIG-1, Biopharmaceutics Quality Review,
(<https://panorama.fda.gov/task/view?ID=5dfb98460002425b1aabbba6d6ace592>)



NGMN Files



4.4.3 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting - Ethinyl Estradiol	 A213950 ConcPK EE.xlsx	 Two Way CalcKe A213950 Fasting EE.	 213950_FASTING_stat_Ethinyl Estradiol	 213950_FASTING_table_Ethinyl Estradiol
Fasting - Norelgestromin	 A213950 ConcPK NGMN.xlsx	 Two Way CalcKe A213950 Fasting NG	 213950_FASTING_stat_Norelgestromin	 213950_FASTING_table_Norelgestromin

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 213950
APPLICANT: Amneal Pharmaceuticals LLC
DRUG PRODUCT: Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg / 35 µg /day

The Division of Bioequivalence III (DBIII) has completed its review and identified the following deficiencies.

1. Your test formulation contains 0.289 mg loading dose of ethinyl estradiol (EE), which is 54.5% of the amount in Reference Standard (RS), Xulane® (0.53 mg per RS labeling). In your pivotal bioequivalence (BE) study (No. ESTN/2018/1607), the test and reference products were applied at the abdomen site. According to a review article, *Pharmacokinetics of a contraceptive patch (Evra™/Ortho Evra™) containing norelgestromin and ethinylloestradiol at four application sites* ([Br J Clin Pharmacol. 2002 Feb; 53\(2\):141-6](#)), absorption of EE during patch application on the abdomen was approximately 20% less than that observed at the other three sites (i.e., buttock, arm, and torso). Please provide adequate evidence to justify that your loading amount of EE is sufficient for the wear period at a non-abdominal application site. Also, please provide your rationale to select 0.289 mg EE loading dose as your final test formulation.
2. Based on the mean concentration-time profile in your pivotal fasting BE study (No. ESTN/2018/1607), we noticed that concentrations of EE dropped significantly in your test product from 72 to 168 hours compared to Xulane®. We have concern that the slower release observed in your test product may be due to the low loading dose of EE which might result in insufficient excess of drug available within the transdermal system (TDS) after 72 hours to maintain the concentration gradient and driving force to sustain the same rate and extent of drug delivery as the reference TDS. Please address our concern.
3. In your pre-study Analytical Method Validation Report (No. 165223APYQ), you mentioned that liquid-liquid extraction and derivatization were used for EE analysis in human plasma. Please provide detailed analytical procedure for extraction and derivatization process. Please also provide detailed analytical procedure involving liquid-liquid extraction with methyl tert-butyl ether procedure for the analysis of Norelgestromin (NGMN).
4. Per your BE summary tables (Table 9A), 31 samples (Test 26, Reference 5) were reanalyzed to obtain confirming value (Code G) for EE. However, per the Bioanalytical Report in Module 5.3.1.4, only 29 samples were listed with Code G, please explain this discrepancy.

5. In your pivotal fasting BE study (No. ESTN/2018/1607), for the EE component, six subjects (Nos. [REDACTED] (b) (6)) had pre-dose concentration greater than 5% of their respective C_{max} in period I. For example, the pre-dose concentration for subject [REDACTED] (b) (6) is 34.68% of the corresponding C_{max} value. In addition, for NGMN component, Subject [REDACTED] (b) (6) had pre-dose concentration in period I which is 44% of the corresponding C_{max} value. Please explain the reason why there are significant pre-dose concentrations in these subjects at period I.
6. To further investigate your failed pilot BE study (No. 16-VIN-0235) and failed pivotal BE study (16-VIN-0236), please submit complete study report, which should include clinical study report, bioanalytical study report, pharmacokinetic and statistical results, concentration/pharmacokinetic dataset in SAS transport format for your failed fasting studies. Also, please provide composition of test formulations used in these studies, including the quantity in mg/patch for each active and inactive ingredient.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

April Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.4.4 Outcome Page

Completed Assignment for 213950 ID:41887

Assessor: Madhusudana Rao Chaluvadi

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Norelgestromin and Ethinyl Estradiol
Transdermal System, 150/35 µg

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Score</i>	<i>Subtotal</i>
41887	12/18/2019	BIO	ANDA Original [1]	1	1
41887	12/18/2019	Complexity	pAUC Statistical Analysis [0.5]	0.5	0.5
41887	12/18/2019	Parallel	Fasting Study [1]	1	1
41887	12/18/2019	Parallel	Fasting Study (Additional Analyte) [0.25]	0.25	0.25
41887	12/18/2019	Parallel	Failed Fasting Study [0.25]	0.25	0.25
41887	12/18/2019	Parallel	Pilot Fasting Study [0.25]	0.25	0.25
41887	12/18/2019	Parallel	Pre-Screening [0.25]	0.25	0.25
				Total:	3.5

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA Number	213950
Drug Name	Norelgestromin and Ethinyl Estradiol TDS, 150/35 mcg per day
Applicant	Amneal Pharmaceuticals LLC
Reference Listed Drug	Xulane [®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day
Indication	Prevention of pregnancy in women who elect to use a transdermal patch.
Date(s)	FDA Received Date: 12/18/2019 Review Assignment Date: 1/8/2020 Statistical Review Goal Date: 4/21/2020
Biometrics Division Statistical Primary Reviewer Statistical Secondary Reviewer	DBVIII Guoying Sun, Ph.D. Wanjie Sun, Ph.D.
Clinical Division Clinical Primary Reviewer Clinical Secondary Reviewer	OGD/OB/DCR Zhuo Zhang, M.D., Ph.D. Michael Spagnola, M.D.
Deficiency Classification	☐ Major ☐ Minor ☒ Not Applicable
Major Deficiency Theme	☐ New Studies Needed ☐ Inconsistent Information ☐ Unresolved Statistical Issues ☒ Other
Justification of Major Deficiency Designation	See Section 4.4 for details
Keywords	Norelgestromin and Ethinyl Estradiol TDS, Adhesion, Irritation/Sensitization, Non-inferiority, Xulane [®]

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY	4
1.1 CONCLUSIONS AND RECOMMENDATIONS	4
1.2 BRIEF OVERVIEW OF THE CLINICAL STUDIES	4
1.2.1 Adhesion Study ESTN/2018/1607.....	5
1.2.2 Irritation and Sensitization Study GCPAMN002.....	5
1.3 FDA STATISTICAL RESULTS AND ISSUES.....	6
2 INTRODUCTION	7
2.1 OVERVIEW	7
2.2 DATA SOURCES	8
3 STATISTICAL EVALUATION	10
3.1 STUDY OVERVIEW – OBJECTIVES, DESIGN, AND ENDPOINTS.....	10
3.1.1 Study Objectives.....	10
3.1.2 Study design	10
3.1.3 Treatments.....	14
3.1.4 Clinical endpoints	14
3.2 SUBJECT DISPOSITION.....	17
3.3 BASELINE DEMOGRAPHICS	21
3.4 STATISTICAL METHODOLOGIES	22
3.4.1 Adhesion Analysis	22
3.4.2 Irritation Analysis	24
3.4.3 Sensitization Analysis.....	25
3.4.4 Additional Analysis	26
3.5 RESULTS AND CONCLUSIONS	27
3.5.1 Applicant’s Analysis Results	27
3.5.2 FDA Reviewer’s Results.....	32
4 SUMMARY AND CONCLUSIONS	36
4.1 SIDE BY SIDE TABLES FOR DCR REVIEWERS.....	36
4.2 STATISTICAL ISSUE AND FINDINGS	37
4.3 CONCLUSIONS.....	37
4.4 COMMENTS TO BE SENT TO THE APPLICANT BY THE REGULATORY PROJECT MANAGER	38
5 REFERENCES	39

LIST OF TABLES

Table 1. Schedule of Assessments / Flow Chart.....	13
Table 2. Dermal Responses.....	16
Table 3. Other Effects.....	17
Table 4. Adhesion Evaluation Scoring Systems.....	17
Table 5. Disposition of Study Population for Adhesion Study ESTN/2018/1607	19
Table 6. Summary of Subject Disposition in I/S Study GCPAMN002.....	19
Table 7. Disposition of Study Population for Irritation/Sensitization Study GCPAMN002.....	20
Table 8. Characteristics of Demographics for Adhesion Study ESTN/2018/1607	21
Table 9. Characteristics of Demographics for Irritation/Sensitization Study GCPAMN002.....	22
Table 10. Applicant’s Frequency Table of Adhesion Scores at Each Time Point by Treatment .	28
Table 11. Applicant’s Non-Inferiority Analysis Result for Mean Adhesion Scores between Treatments.....	29
Table 12. Applicant’s Proportion of subjects with An Adhesion Score ≥ 2 at Any Time Point between Treatments	29
Table 13. Applicant’s Proportion of Subjects with Test Product Mean Adhesion Score Greater Reference Product by 1 or More, Compared to Proportion of Subjects with Reference Product Mean Adhesion Score Greater Than Test Product by 1 or More	29
Table 14. Applicant’s Time to an Adhesion Score ≥ 2 between Treatments	30
Table 15. Applicant’s Analysis of Mean Irritation Score (Per-Protocol Population for Irritation)	30
Table 16. Applicant’s Summary of Sensitization Reactions at Challenge Phase (Per-Protocol Population for Sensitization).....	31
Table 17. FDA’s Analysis for the Mean Adhesion Scores using Mixed Model (PPPA) (N=83)	32
Table 18. FDA’s Proportion of Subjects with an Adhesion Score ≥ 2 at Any Time Point.....	32
Table 19. FDA’s Proportion of Subjects with MAS Difference of 1 or More for PPPA	32
Table 20. FDA’s Descriptive Statistics for Mean Irritation Scores for PPPI (N=211).....	33
Table 21. FDA’s Number and Frequency (%) of Combined Irritation Score (PPPI, N=211).....	33
Table 22. FDA’s Analysis for the Mean Irritation Scores Using Mixed Model (PPPI) (N=211)	34
Table 23. FDA’s Analysis on Proportion of Subjects with an Adhesion Score ≥ 2 at Any Time Point (PPPI) (N=211).....	34
Table 24. FDA’s Frequency of irritation scores for the Challenge period (PPPS).....	35
Table 25. Adhesion Analysis Results (Mean Adhesion Score) for PPPA by Applicant and FDA	36
Table 26. Irritation Analysis Results (Mean Irritation Score) for PPPI by Applicant and FDA ..	36
Table 27. Justification of Major Deficiency Designation.....	38

1 EXECUTIVE SUMMARY

The purpose of this review is to assess the irritation, sensitization, and adhesion properties of the Test patch- Norelgestromin and Ethinyl Estradiol Transdermal System (TDS) 150/35 mcg per day, manufactured by Amneal Pharmaceuticals LLC, versus the Reference patch – Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day, manufactured by Mylan Pharmaceuticals Inc., among healthy, non-pregnant, non-lactating females under fasting conditions. The applicant submitted two studies: Adhesion Study ESTN/2018/1607, and Irritation/Sensitization Study GCPAMN002 to support this application.

1.1 Conclusions and Recommendations

Skin Irritation: The non-inferiority of the Test versus the Reference product was established using the mean combined irritation scores from the Induction Phase of the Irritation/Sensitization study GCPAMN002.

The statistical review and evaluation of the data submitted for ANDA 213950 Irritation/Sensitization Study GCPAMN002 support approval for irritation.

Skin Sensitization: The Test product was shown to be no more sensitizing than the Reference product using the proportion of potential sensitization from the Challenge Phase of the Irritation/Sensitization study GCPAMN002.

The statistical review and evaluation of the data submitted for ANDA 213950 Irritation/Sensitization Study GCPAMN002 support approval for sensitization.

Patch Adhesion: Non-inferiority of the Test versus the Reference product was established using the mean adhesion scores from the Adhesion study ESTN/2018/1607. The statistical review and evaluation of the data submitted for ANDA 213950 Adhesion Study ESTN/2018/1607 support approval for adhesion.

1.2 Brief Overview of the Clinical Studies

This application consists of two studies: Adhesion Study ESTN/2018/1607, and Irritation/Sensitization Study GCPAMN002.

1.2.1 Adhesion Study ESTN/2018/1607

This was an open-label, balanced, randomized, single-application, two-treatment, two-sequence, two-period, two-way crossover study comparing the adhesive properties of the Test patch relative to those of the Reference patch. This study was conducted in two cohorts, i.e., Cohort 1: Subject No. (b) (6) (started on 3/9/2019); Cohort 2: Subject No. (b) (6) started on 3/26/2019). In this study, Single application (One patch of Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day) of test or reference product was applied on the subject's clean, dry area on abdomen by trained study personnel in each study period. In Period 1, the first patch was applied within seven days after the first day of a menstrual period of both the cohorts. In Period 2, patch application was done after 21 (for Cohort 1) or 20 (for Cohort 2) days washout from the last PK blood draw of the first period. The patch was removed after 07 days (at 168.00 hours) of application in each study period. Adhesion scoring was done immediately after patch application (0 hours) and at 24, 48, 72, 96, 120, 144, and 168 hours post patch application.

There were eighty four (84) female subjects planned and enrolled for the study. Out of eighty-four (84) dosed subjects, seventy nine (79) subjects completed both the periods. Adhesion assessment analyses were performed based on the Per Protocol Population for Adhesion (PPPA): eighty-three (83) subjects (N=80 for Test and 82 for Reference).

1.2.2 Irritation and Sensitization Study GCPAMN002

This was a randomized, controlled, within-subject study to compare the skin irritation and sensitization potential of a generic Norelgestromin and Ethinyl Estradiol TDS, 150/35 µg/day to that of Xulane[®] (norelgestromin and ethinyl estradiol TDS, 150/35 µg/day) in healthy, non-pregnant, non-lactating females, who were candidates for hormonal contraception. As recommended by the Draft Guidance on Norelgestromin and Ethinyl Estradiol TDS, half (1/2) cut patch of the Test formulation and half (1/2) cut patch of the Reference formulation was applied to the upper outer arms as a site of application during the induction/irritation and the Challenge/Sensitization Phases for all applications. The study was conducted at one clinical location.

A total of 280 subjects were screened and 220 subjects were randomly assigned to treatment. Of these, 201 (91.4%) subjects completed the study, while 19 (8.6%) subjects discontinued. The Per Protocol Population for Irritation (PPPI) included 211 subjects (N = 211 for Test, N = 211 for Reference). The Per Protocol Population for Sensitization (PPPS) included 205 subjects (N = 205 for Test, N = 205 for Reference).

1.3 FDA Statistical Results and Issues

Adhesion Study ESTN/2018/1607

The primary endpoint (mean adhesion scores) was analyzed using a mixed linear model after incorporating the cohort effect. Data from 83 subjects (80 Test patches and 82 Reference patches) were included in the primary analyses utilizing the PPPA. The 95% upper confidence bound (UCB) for the difference of the T and R mean adhesion score ($\mu_T - \mu_R$) was -0.01160, which is less than the non-inferiority margin for adhesion: 0.15. Therefore, the non-inferiority of the Test product to the Reference product was demonstrated regarding the primary endpoint mean adhesion score using PPPA in the Adhesion Study ESTN/2018/1607.

Irritation and Sensitization Study GCAPMN002

Irritation

The primary endpoint (mean irritation score) was analyzed using a mixed linear model. The non-inferiority analyses based on the mean irritation scores showed that the one-sided 95% upper confidence bound (UCB) for the difference of the T and R mean adhesion score ($\mu_T - \mu_R$) was 0.0031, which was less than the non-inferiority margin for irritation: 0.2. Therefore, non-inferiority was established for the Test patch versus the Reference patch in the primary endpoint mean irritation score using PPPI in the Irritation and Sensitization Study GCAPMN002.

Sensitization

In the Challenge Phase, no subjects from either treatment groups demonstrated a potential sensitization reaction to the Reference patch or Test patch. Therefore, non-inferiority was established for the Test patch versus the Reference patch in sensitization potential using PPPS in the Irritation and Sensitization Study GCAPMN002.

No major statistical issues were identified in this ANDA application.

2 INTRODUCTION

2.1 Overview

Anneal Pharmaceuticals LLC is developing a generic transdermal product formulation containing Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day, Test Product, as a pharmaceutical equivalence to Mylan's Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day, Reference Product. As part of the approval requirements for generic topical patch products, applicants are required to demonstrate that their topical patch, when applied for multiple applications, does not have the potential to induce more irritation or more occurrences of skin sensitization than the corresponding reference listed drug; and to ensure that the generic product adheres to the skin as well as the Reference over the intended duration of wear. This review focuses on two studies, i.e., Adhesion Study ESTN/2018/1607 and Irritation/Sensitization Study GCAPMN002, to evaluate the non-inferiority of the Test product as compared to the Reference product in adhesive properties and skin irritation and sensitization potential.

Reference Drug

Xulane[®] is an Estrogen/ Norelgestromin combination hormonal contraceptive (CHC) manufactured by Mylan Technologies. It was the first generic version of Janssen Pharmaceuticals Inc.'s Ortho Evra[®] (Norelgestromin / Ethinyl Estradiol Transdermal System 150/35 mcg per day) (discontinued) and Xulane[®] was approved on 4/16/2014 (ANDA #200910). Xulane[®] is indicated for the prevention of pregnancy in women who elect to use a transdermal patch.

FDA's Guidances

This review is based on the recommendations in the following guidances:

- OGD's product specific guidance (PSG): *Draft Guidance on Ethinyl Estradiol; Norelgestromin (2019)*
(https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf);
- OGD's 2018 draft guidance for patch adhesion: *Assessing Adhesion with Transdermal and Topical Delivery Systems (TDS) for ANDAs*
(<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry>);

- OGD’s 2018 draft guidance for patch irritation and sensitization: *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>).

2.2 Data Sources

The applicant’s submissions are stored in Electronic Document Room (EDR). The study reports and the data sets used for this statistical review are at the following locations.

Adhesion Study ESTN/2018/1607:

Clinical Study Reports: <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\estn-2018-1607-fast\study-report-body.pdf>

Protocol: <\\cdsesub1\evsprod\anda213950\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\estn-2018-1607-fast\protocol.pdf>

Statistical Analysis Plan <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\estn-2018-1607-fast\statistical-methods.pdf>

SAS Data Sets:

<\\cdsesub1\evsprod\anda213950\0002\m5\datasets\estn-2018-1607-fast\analysis\adam\datasets\adad.xpt>

<\\cdsesub1\evsprod\anda213950\0003\m5\datasets\estn-2018-1607-fast\analysis\adam\datasets\adadlocf.xpt>

Irritation/Sensitization Study GCPAMN002:

Clinical Study Reports: <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\gcpamn002-fast\gcpamn-002-study-report-body.pdf>

Protocol: <\\cdsesub1\evsprod\anda213950\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\gcpamn002-fast\16-1-1-protocol-and-amendment.pdf>

Statistical Analysis Plan: <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\gcpamn002-fast\16-1-9-statistical-methods.pdf>

SAS Data Sets: [\\cdsesub1\evsprod\anda213950\0002\m5\datasets\gcpamn002-fast\analysis\adam\datasets\adis.xpt](#)
[\\cdsesub1\evsprod\anda213950\0002\m5\datasets\gcpamn002-fast\analysis\adam\datasets\adsl.xpt](#)

3 STATISTICAL EVALUATION

3.1 Study Overview – Objectives, Design, and Endpoints

3.1.1 Study Objectives

Adhesion Study

- To evaluate the relative adhesive properties of a Test Norelgestromin and Ethinyl Estradiol TDS (manufactured by: Amneal Pharmaceuticals LLC) compared to those of the Xulane[®] (norelgestromin and ethinyl estradiol transdermal system, manufactured for Mylan Pharmaceuticals Inc) 150/35mcg per day in healthy, adult, human female subjects under fasting conditions.

Irritation/Sensitization Study

- To demonstrate the non-inferiority of the Test Product compared to the Reference product with regard to irritation and sensitization potential in healthy females.

3.1.2 Study design

Adhesion Study ESTN/2018/1607

This was a randomized, open label, balanced, two treatment, two period, two sequence, single application, one-site, crossover design study comparing the adhesive properties of the Test patch relative to those of the Reference patch. The study was conducted with 84 healthy adult female subjects in accordance with protocol version 02, and protocol amendment 01 to final protocol version 02.

There were eighty-four (84) female subjects planned and enrolled for the study. Study was conducted in two cohorts i.e. Subject No. (b) (6) in cohort I (started on 3/9/2019); and Subject No. (b) (6) in cohort II (started on 3/26/2019). Patch application was done for all eighty-four (84) enrolled subjects in period I. After confirmation of the compliance criteria on check-in day, subjects housed in the clinical facility at least 11.50 hours prior to patch application and remained in-house until 168.00 hours post-application in the study.

After final screening and additional safety measures, first patch was applied within seven days of initiation of menstrual period.

On day of patch application, under fasting condition, single patch of test formulation (Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day) or reference formulation (Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day) was applied on the subject's clean and dry area on abdomen by the trained personnel as per the randomization schedule in each study period at ambient temperature in semi recumbent position.

The TDS administered in the second study period was applied by the same trained patch applicants to the same anatomical site as in the first study period, but on the contralateral side of the body. Adhesion scoring was done immediately after patch application (00.00 hours) and at 24.00, 48.00, 72.00, 96.00, 120.00, 144.00, and 168.00 (just prior to patch removal) hours post patch application. Adhesion scoring was performed within $\pm$ 10 minutes of the above mentioned scheduled time. The patches were checked for degree of adhesion. Degree of patch adhesiveness was rated and recorded by the PI in both the study periods of both the cohorts.

No adhesive tape, overlays, bandages or similar products were applied during the application period.

Patch was removed at 168.00 hours after the application (with a window of +5 minutes)

Irritation/Sensitization Study GCPAMN002

This was a randomized, controlled, one-site, within-subject study to compare the skin irritation and sensitization potential of a generic Norelgestromin and Ethinyl Estradiol TDS, 150/35 $\mu\text{g}/\text{day}$ to that of Xulane[®] (norelgestromin and ethinyl estradiol TDS, 150/35 $\mu\text{g}/\text{day}$) in healthy, non-pregnant, non-lactating females, who were candidates for hormonal contraception.

The study consisted of the following phases:

- Induction/Irritation Phase
- Rest Phase
- Challenge/Sensitization Phase
- Re-challenge Phase

Following screening, female subjects were given oral contraceptive tablets containing Medroxyprogesterone 2.5 mg for up to 12 days to synchronize the menstrual cycles. Documentation of compliance of oral contraceptive dosing was based on the subject diary. All study subjects were synchronized using the same brand of Medroxyprogesterone 2.5 mg.

Induction/Irritation Phase

Subjects returned to the clinical facility within 7 days of initiation of their menstrual period for the Induction Phase of the study. Test and Reference patch/systems (1/2 of each) were applied concurrently on the subject's contralateral upper outer arms and replaced, as noted below every 7 days, for a total of 3 applications over 21 days. Patch applied on Day 1 was removed on Day 8, patch applied on Day 8 was removed on Day 15, and patch applied on Day 15 was removed on Day 22.

The Test treatment was applied to one side of the contralateral upper outer arm and the Reference Treatment was applied to the other side, according to a computer-generated randomization schedule. The randomization schedule was generated such that approximately half of the subjects had the test patch applied to their right arm and the approximately half to their left arm.

On Day 1 prior to the first application (baseline assessment) and on Days 8 (± 2 hours), 15 (± 2 hours), and 22 (± 2 hours), a trained evaluator observed the application sites for any signs of local irritation using the “dermal response” and “other effects” rating scales. At every visit and before patch/system removal, the adhesion of all patch/systems was assessed to ensure they were in good contact with the skin. At each visit, subjects were questioned about both local and general adverse events (AEs) and their health status was monitored.

Rest Phase

After removal of the last patch/system on Day 22, a 14- to 17-day patch-free rest period was given when no patches/systems were applied.

Challenge/ Sensitization Phase

Eligible subjects entered the Challenge/ Sensitization Phase of the study to evaluate the sensitization potential of the patch/systems when applied for a single 48-hour application period. During this phase, one half ($\frac{1}{2}$) of both the Test and Reference patch were applied on Day 36 to a naive site on the subject's contralateral arms. Each patch was applied to the same side (left/right) that was used in the Induction/Irritation Phase for treatment, using the same randomization schedule, but at least 1 inch below the site of application used during the Induction/Irritation Phase. The patches were removed on Day 38 at least 48 hours (+ 2 hours) after application or until excessive local reaction occurs, and the application area was evaluated for possible skin sensitization effects over the next 72 hours. Sensitization evaluations were performed at 30 (± 10) minutes, 24 (± 1) hours, 48 (± 2) hours, and at 72 (± 3) hours after removal. Before patch removal on Day 38, at least 48 (+2) hours after application or until removal because of excessive local reaction, the adhesion of the patch was assessed to ensure the patch was in good contact with the skin.

Irritation study: Induction period (Study Days 1 to 22)	Rest period (14-17 days)	Sensitization study: Challenge period (Study Days 36 to 41)

Re-challenge Phase

If the Investigator was not able to make a definitive diagnosis of sensitization, then subjects who showed a potential sensitization response to a patch/system during the Challenge/Sensitization Phase, were to be re-challenged 4 to 8 weeks after the end of the Challenge Phase to confirm the sensitization reaction. In such a case, one of the same patch treatments was applied to the subject's contralateral upper outer arms. The patch was to be applied to the same side of the body (left/right) that was used in the Induction/Irritation Phase, using the same randomization schedule, except the patch was applied to the contralateral upper outer arms. The patch was to be removed at least 48 (+2) hours after application or until removal because of excessive local

reaction, and the application area was evaluated for potential skin sensitization effects over the next 72 hours. Sensitization evaluations were to be performed at 30 ($\pm$ 10) minutes, 24 ($\pm$ 1) hours, 48 ($\pm$ 2) hours, and at 72 ($\pm$ 3) hours after removal. Before patch removal, the adhesion of the patch was to be assessed to ensure the patch was in good contact with the skin.

Safety assessments included AE monitoring, vital signs, electrocardiogram (ECG), clinical laboratory testing, application site evaluation, and physical examination. A Pap smear was to be performed at the Investigator's discretion if the subject did not have a normal Pap within the previous 3 years. The United States Preventive Services Task Force recommends screening for cervical cancer in women ages 21 to 65 years, inclusive, with cytology (Pap smear) every 3 years. Gynecological examination included breast examination at the time of screening.

The details of assessments in Induction/Sensitization study are as in Table 1.

Table 1. Schedule of Assessments / Flow Chart

Visit Name / Activity	Screening	Induction		Rest	Challenge/Sensitization			End of Study
		Day 1	Days 8, 15, 22		14- to 17- day	Day 36	Day 38	
Informed consent	X							
Medical history and demographic data	X							
Brief physical examination	X							X
Inclusion/exclusion criteria	X							
Inclusion/exclusion update		X						
Subject status update		X	X		X	X	X	X
Vital signs ^a	X	X	X		X	X	X	X
Drug and alcohol screen ^a	X	X	X		X	X	X	X
Serum pregnancy test	X							
Urine pregnancy test ^a		X	X		X	X	X	X
12-lead Electrocardiogram	X							X
Clinical laboratory test	X							X
Prior and concomitant	X	X	X		X	X	X	X
Patch application/		X	X		X			
Patch removal ^b			X			X		
Adhesion assessment ^c			X			X		
Irritation/sensitization		X	X		X	X	X	X
Adverse events ^a		X	X		X	X	X	X

Source: Table 3 in GCPAMN002-Clinical Study Report

- a. Performed as specified in Section 9.5.1.2.
- b. Patches/systems were applied/replaced and removed (as applicable) as specified in Section 9.4.
- c. Irritation/Sensitization and adhesion assessments were performed as specified in Section 9.5.1.1.

3.1.3 Treatments

Studies ESTN/2018/1607 and GCPAMN002

Test:	Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per Day Manufactured by: Amneal Pharmaceuticals LLC Batch No.: PW-ST-18020A Manufacture Date: 10/02/2018 Expiry Date: 10/2019
Reference:	Xulane [®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day Manufactured for: Mylan Pharmaceuticals Inc. Batch No.: 3098718 Manufacture Date: N/A Expiry Date: 04/2020

3.1.4 Clinical endpoints

Adhesion Analysis (Study ESTN/2018/1607)

Primary Endpoint:

The applicant used the same primary endpoint as that recommended in OGD's 2018 Guidance for TDS adhesion¹. The primary endpoint for evaluating adhesion was the Mean Adhesion Score (MAS) during the 7-day application period for each patch. The MAS for a specific subject and patch type was derived from individual adhesion scores at each assessment time point 24.00, 48.00, 72.00, 96.00, 120.00, 144.00 and 168.00 hours averaged across all the equally spaced (24-hour) time points (except the baseline [0-hour] time point).

Other Endpoints:

The applicant used the same other endpoints as those recommended in the OGD's 2018 Guidance for TDS adhesion¹.

“FDA recommends that applicants perform the following descriptive analyses for the evaluation of TDS adhesion (using the five-point adhesion scale in Table 4) to assess the possible treatment group differences in potentially clinically meaningful values or events:

¹ [Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry)
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry>

1. Proportion of subjects with an adhesion score ≥ 2 at any time point, compared between T and R.
2. Proportion of subjects with a T mean adhesion score greater than the corresponding R mean adhesion score by 1 or more, compared to the proportion of subjects with an R mean adhesion score greater than the corresponding T mean adhesion score by 1 or more.
3. Time to an adhesion score >2 compared between T and R. If there are a sufficient number of events, a Kaplan Meier cumulative incidence can be plotted.

Irritation Analysis (Study GCPAMN002)

Primary Endpoint:

The applicant used the same primary endpoint as that recommended in the OGD's 2018 Guidance for TDS irritation and sensitization²

The primary endpoint of irritation was the mean Irritation Score (MIS). At each assessment time point for each subject and for each product, a combined irritation score was calculated as adding the "dermal response" (Table 1) score and the numeric equivalent for "other effects" (Table 2). For each subject and each product, the MIS was calculated as the sum of the combined irritation scores recorded at 30 minutes (± 10 minutes) after patch removal on Day 8, 15, and 22, divided by the total number of assessments.

Other Endpoints:

In addition to the primary endpoint, the applicant evaluated the following other endpoints which are consistent with the recommendation of the OGD's 2018 Guidance for TDS irritation and sensitization².

- a. Total number of observations with a combined "dermal response" and "other effects" irritation score of 3 or more for each patch type.
- b. Number of patches that were moved or removed due to an unacceptable degree of irritation for each patch type.
- c. Number of days until patch was removed due to an unacceptable degree of irritation for each patch type.
- d. The proportion of subjects by subject/system for each of the irritation scores (0, 1, 2, and ≥ 3).

² *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018*
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>

Sensitization Analysis (Study GCPAMN002)

Both the applicant and FDA used the proportion of subjects showing a potential sensitizing reaction during the Challenge Phase as the primary endpoint, which is recommended by OGD's the OGD's 2018 Guidance for TDS irritation and sensitization³

Consider a subject to be potentially sensitized if all the following criteria are met:

- a. The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the challenge phase patch.
- b. The subject has a combined "dermal response" and "other effects" numeric score of at least 2 at their last evaluation during the challenge phase.
- c. The above two criteria were met during both the challenge phase and the re-challenge phase, if the subject completed a re-challenger phase.

Rating Scale

Irritation Scale:

The applicant used the same irritation scale as that recommended in the OGD's 2018 Guidance for TDS irritation and sensitization³: Tables 2 and 3 show the 'dermal response' and 'other effects' rating scales for irritation. The statistical analysis is based on the combined irritation score by adding the 'dermal response' score and the numeric equivalent for 'other effects' letter score. The applicant used the same irritation scale.

Table 2. Dermal Responses

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema that is barely perceptible	1
Definite erythema that is readily visible and minimal edema or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond the application site	7

³ *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018*

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>

Table 3. Other Effects

Observation	Score (Numerical Equivalent)
Slightly glazed appearance	A (0)
Markedly glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the TDS site	G (3)
Small petechial erosions and/or scabs	H (3)

Adhesion Scale:

The applicant used the same adhesion scale as recommended in the OGD’s 2018 Guidance for TDS adhesion¹ (Table 4).

Table 4. Adhesion Evaluation Scoring Systems

Patch Adhesion Situation	Score
≥ 90% adhered (essentially no lift off of the skin)	0
≥ 75% to < 90% adhered (some edges only lifting off of the skin)	1
≥ 50% to < 75% adhered (less than half of the patch lifting off the skin)	2
< 50% adhered but not detached (more than half of the patch lifting off of the skin without falling off)	3
patch detached (patch completely off the skin)	4

3.2 Subject Disposition

Based on FDA’s guidance, the adhesion, irritation, and sensitization analysis populations are defined as follows. The applicant followed the recommendation on the per-protocol (PP) population in OGD’s guidances⁴. FDA statistical reviewers and the applicant had the same PPPA, PPPI, and PPPS.

⁴ *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018*
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>
Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry>

PP Population for Adhesion (PPPA) – PPPA included all patches except those removed early for unacceptable irritation or those that dropped out of the study before the end of the 7-day application for reasons unrelated to adhesion (e.g., because of a protocol violation).

PP Population for Irritation (PPPI) – PPPI included all the patches applied sequentially to the same anatomical site for the entire 21-day induction phase without any period of detachment longer than 24 hours. If a patch was moved or removed because of excessive irritation and without significant protocol deviations, it would be included in the PP population, using the LOCF from the original application site.

PP Population for Sensitization (PPPS) – PPPS included subjects with all scheduled patch applications/removals completed in the induction/irritation phase of the study for a specific patch, had the patch applied (Day 36) for at least 48 hours (+ 2 hours) (or until removal due to excessive local reaction and/or irritation before Day 38), had at least one irritation assessment performed after 24 hours (at either 48 or 72 hours) post-removal during the challenge/sensitization and/or re-challenge phase, and completed without significant protocol deviations. If a Test patch is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.

Adhesion Study ESTN/2018/1607

Table 5 shows that there were eighty-four (84) female subjects planned and enrolled for the study. Patch application was done for all eighty-four (84) enrolled subjects in period I. Out of eighty four (84) dosed subjects, seventy nine (79) subjects completed both the periods of study. Adhesion analysis was performed on 80 patches for the Test product and 82 patches for the Reference product, which pertain to 83 subjects in total. One subject (Subject (b) (6)) voluntarily withdrew her consent from the study after 04.00 hours post patch application during period I. Four Test patches were excluded from PPPA due to not turning up (n=2) or withdrawn from the study (n=2). Two Reference patches were excluded from PPPA due to withdrawn from the study.

Table 5. Disposition of Study Population for Adhesion Study ESTN/2018/1607

Populations	FDA and Applicant	
	Test	Reference
Total Randomized Subjects	84	84
PPPA	80	82
Total exclusion from PPPA	4	2
Reason for exclusion from PPPA		
Subject didn't turn up for study period	2	0
Subject was withdrawn from the study	2	2

Irritation Analysis (Study GCPAMN002)

Table 6 shows that a total of 280 subjects were screened and 220 subjects were randomly assigned to treatment. Of the 220 randomized subjects, 201 (91.4%) subjects completed the study and 19 (8.6%) subjects discontinued. Overall, the primary reasons for study discontinuation were withdrawal of subject consent (13 subjects) followed by lost to follow-up, positive drug screen and other reasons (2 subjects each). The two 'other reasons' reported included one subject unable to make other study dates due to last minute decision and the other subject not completing the study due not completing Visit Day 40 and Day 41.

Table 6. Summary of Subject Disposition in I/S Study GCPAMN002

Disposition	Overall (N=280)
	n (%)
Screened subjects	280
Screen failure subjects	36
Non-randomized subjects	24
Randomized subjects	220
Completion status	
Completed the study	201 (91.4)
Discontinued early from study	19 (8.6)
Primary Reasons for Discontinuation from Study ^a	
Adverse event	0
Lost to follow-up	2 (10.5)
Subject withdrew consent	13 (68.4)
Pregnancy	0
Protocol violation	0
Principal investigator decision	0
Termination of the study	0
Positive alcohol breath test	0
Positive drug screen	2 (10.5)
Other	2 (10.5)

Source: Table 4 in applicant's clinical study report GCPAMN-002

N = Number of all screened subjects. Percentages were based on the number of randomized subjects.

^a Percentages for discontinuation reasons were based on the number of subjects who discontinued early from the study.

Table 7 shows the disposition of the study population for the Irritation/Sensitization Study GCPAMN002. For irritation, among the 220 randomized subjects, the Per Protocol Population for Irritation (PPPI) included 211 subjects (211 Test patches and 211 Reference patches); 9 subjects were excluded from PPPI due to lost to follow-up (n=2), subject withdrawing consent (n=4), positive drug screen (n=2) and other reasons (n=1). For sensitization, among the 220 randomized subjects, the Per Protocol Population for Sensitization (PPPS) included 205 subjects (205 Test patches and 205 Reference patches); 15 subjects were excluded from PPPS due to lost to follow up (n=2), subject withdrawing consent (n=10), positive drug screen (n=2), and other reasons (n=1).

Table 7. Disposition of Study Population for Irritation/Sensitization Study GCPAMN002

Populations	FDA and Applicant	
	Test	Reference
Total Randomized Population	220	220
PPPI	211	211
Total exclusion from PPPI	9	9
Reason for exclusion from PPPI		
Lost to follow-up	2	2
Subject withdrew consent	4	4
Positive drug screen	2	2
Other	1	1
PPPS	205	205
Total exclusion from PPPI	15	15
Reason for exclusion from PPPI		
Lost to follow-up	2	2
Subject withdrew consent	10	10
Positive drug screen	2	2
Other	1	1

Resource: Reviewer's analysis

3.3 Baseline Demographics

Table 8 summarizes the distributions of age, gender, and race for the PPPA in the Adhesion Study ESTN/2018/1607. The 83 subjects in the PPPA population were all female, Asian, and on average 30 years old.

Table 8. Characteristics of Demographics for Adhesion Study ESTN/2018/1607

		PPPA (N=83)	
		Test (N=80)	Reference (N=82)
Age (years)			
Mean (Std)		30.31(2.63)	30.22(2.62)
Median (Range)		31(22-34)	31(22-34)
Gender			
Female		80 (100%)	82 (100%)
Race			
Asian		80 (100%)	82 (100%)

Resource: Reviewer's Analysis

Table 9 summarizes the distributions of age, gender, and race for the PPPI and PPPS in the Irritation/Sensitization Study GCPAMN002. The 211 subjects in the PPPI population were all female, 88.2% Black or Africa American, 11.4% White, 0.5% with multiple races, and on average 28 years old. Among the 211, 8% were Hispanic or Latino and 92% were not Hispanic or Latino.

The 205 subjects in the PPPS population were all female, 88.3% Black or Africa American, 11.2% White, 0.5% with multiple races, and on average 28 years old. Among the 205, 7.8% were Hispanic or Latino and 92.2% were not Hispanic or Latino.

Table 9. Characteristics of Demographics for Irritation/Sensitization Study GCPAMN002

	Irritation (N= 211)	Sensitization (N= 205)
Age (years)		
Mean (Std)	27.65 (4.34)	27.70 (4.28)
Median (Range)	29 (18-35)	29 (18-35)
Gender		
Female	211 (100%)	205(100%)
Race		
Black or Africa American	186 (88.15%)	181 (88.29%)
Multiple	1 (0.47%)	1 (0.49%)
White	24 (11.37%)	23 (11.22%)
Ethnicity		
Hispanic or Latino	17 (8.06%)	16 (7.80%)
Not Hispanic or Latino	194 (91.94%)	189 (92.20%)

3.4 Statistical Methodologies

3.4.1 Adhesion Analysis

Both the applicant and the FDA statistical reviewers followed the statistical recommendation of OGD’s 2018 draft guidance for TDS adhesion⁵. However, the FDA statistical reviewers and the applicant had minor differences in the statistical model to adjust for the two cohorts as a group effect.

Primary Endpoint:

In OGD’s 2018 draft guidance for TDS adhesion⁶, the recommended primary endpoint for evaluating adhesion of TDS is the mean adhesion score derived for a TDS from individual adhesion scores at each assessment time point averaged all the equally spaced time points except the baseline or time 0.

⁵ [Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry)
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry>

⁶ [Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry)
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-adhesion-transdermal-delivery-systems-and-topical-patches-andas-draft-guidance-industry>

If scores from unequally spaced time points are available, a weighted average $\bar{x}_w$, with weights corresponding to interval length, may be calculated as follows:

$$\bar{x}_w = \sum_{i=1}^n w_i x_i \quad \text{where } w_i = \frac{(t_i - t_{i-1})}{T}$$

Here, $\bar{x}_w$ is the observed weighted mean adherence score for a TDS across n unequally-spaced time points after the baseline, x_i is the observed adherence score at the i^{th} measurement, w_i is the corresponding weight for x_i , T denotes the total duration of wear, t_i denotes the i^{th} measurement time, and t_{i-1} denotes the preceding $(i-1)^{\text{th}}$ measurement time.

To test the non-inferiority of the Test (T) product compared to the Reference Listed Drug (R) product, the guidance recommends evaluating the difference in mean adherence scores across the study duration, with a non-inferiority margin of 0.15 ($\delta = 0.15$). The hypotheses tested at the significance level of 0.05 are:

$$H_0: \mu_T - \mu_R > \delta \quad \text{vs.} \quad H_1: \mu_T - \mu_R \leq \delta,$$

where μ_T and μ_R are the overall mean of T and R adherence scores, respectively, and the alternative hypothesis H_1 represents the non-inferiority of T relative to R with regard to adherence.

Applicant:

The 90% confidence interval was constructed for the difference in least-squares means of the test and reference treatment Mean Adherence Scores (MAS) using Analysis of Variance (ANOVA) model. PROC GLM was used with Group, Sequence, Group*Sequence, Period (Group), Treatment, and Group*Treatment as fixed effect terms and Subject (Group*Sequence) as a random effect term. If the Group*Treatment effect was found to be statistically insignificant at 5% level, then this interaction term (Group*Treatment) was dropped from the model and statistical analyses were re-performed excluding this interaction term. The SAS Estimate statement was used to obtain an estimate and the upper limit of the 90% confidence interval (upper 95% confidence bound) for the test-to-reference difference.

FDA:

The 90% confidence interval was constructed for the difference in least-squares means of the test and reference treatment Mean Adherence Scores (MAS) using the Linear Mixed model. The Mixed model included Group, Sequence, Group*Sequence, Period (Group), Treatment, and Group*Treatment as fixed effect terms and Subject nested within Group*Sequence as a

random effect term. If the Group*Treatment effect was found to be statistically insignificant at 10% level, then this interaction term (Group*Treatment) was dropped from the model and statistical analyses were re-performed excluding this interaction term.

Other Endpoints:

In addition to the primary endpoint, FDA recommends the following secondary endpoints were assessed for evaluation of adhesion (descriptive statistics only):

- Proportion of subjects with an adhesion score ≥ 2 at any time point, compared between test and reference products.
- Proportion of subjects with a test product mean adhesion score greater than the corresponding reference product mean adhesion score by 1 or more, compared to the proportion of subjects with a reference product mean adhesion score greater than the corresponding test product mean adhesion score by 1 or more.
- Time to an adhesion score ≥ 2 compared between test and reference products. If there were a sufficient number of events, a Kaplan Meier cumulative incidence was to be plotted.

3.4.2 Irritation Analysis

Both the applicant and the FDA statistical reviewers followed the statistical recommendation of OGD's 2018 draft guidance for TDS irritation/sensitization⁷. However, the FDA statistical reviewers and the applicant had minor differences in the statistical model.

The primary endpoint of irritation was the individual mean Irritation Score (MIS) (“dermal response” + “other effects”) recorded during the 21-day continuous application period (i.e., the MIS for a specific subject and patch was the sum of all of the valid Irritation Scores (IS) recorded at 30 minutes ($\pm$ 10 minutes) after patch removal on Days 8 + 15 + 21, divided by the total number of valid irritation assessments).

To demonstrate the non-inferiority (NI) of the Test product compared to the Reference product with respect to the MIS, the Test product should be shown to be statistically non-inferior to the

⁷ *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018*
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>

Reference product based on evaluating the difference in the Test and Reference products' overall mean MIS, with an NI margin of 0.20 ($\delta = 0.20$).

The appropriate parametric hypotheses using MIS are:

$$H_0: \mu_T - \mu_R \geq \delta \text{ (not non-inferior)}$$

$$H_1: \mu_T - \mu_R < \delta \text{ (non-inferior)}$$

Applicant:

In the applicant's analysis of variance (ANOVA) model, they used MIS as dependent variable, left arm treatment-right arm treatment as sequence, treatment as main effects along with subject nested in sequence as random effect in a 'Proc Mixed' procedure.

FDA:

FDA statistical reviewers used a linear mixed model where MIS was the dependent variable, left or right arm (where the patch is applied) and treatment were included as fixed effects and subject nested as a random effect.

3.4.3 Sensitization Analysis

Both the applicant and the FDA statistical reviewers followed the statistical recommendation of OGD's 2018 draft guidance for TDS irritation/sensitization⁸.

Subjects are considered to have demonstrated a potential sensitization response for a specific patch by the irritation rating scales if the following criteria are met:

1. The subject has at least one irritation assessment occurring at more than 24 hours (i.e., at 48 or 72 hours) after the removal of the challenge phase patch.
2. The subject has an Irritation Score ("dermal response" + "other effects") that is 2 or more at the last evaluation during the challenge phase.
3. The above two criteria were met during both the challenge phase and the re-challenge phase, if the subject completed a re-challenge phase.

⁸ *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs, Guidance for Industry, Oct 2018*

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-irritation-and-sensitization-potential-transdermal-and-topical-delivery-systems-andas>

3.4.4 Additional Analysis

In addition, the FDA statistical reviewers conducted the McNemar test for other endpoints such as the proportions of clinically significant irritation, sensitization or adhesion (“event”), which are correlated dichotomous data in a cross-over or matched pairs study. The McNemar test was used to compare the difference between the matched Test and the Reference proportions.

<Matched pairs dichotomized analysis>

Let

p_T = rate of the Test, p_R = rate of the Reference (p_T and p_R might be irritation rates, sensitization rates, or adhesion rates depending on the analysis);

n = total number of subjects;

b = number of subjects with a negative outcome (irritation, sensitization, or detachment) using the Test but not the Reference;

c = number of subjects with a negative outcome (irritation, sensitization, or detachment) using the Reference but not the Test.

Hypotheses: $H_0: p_T - p_R > \delta$ vs $H_1: p_T - p_R \leq \delta$

Data on two outcomes from matched pairs

		Reference	
		Score $\geq$ crit*	Score<crit
Test	Score $\geq$ crit	a	b
	Score<crit	c	d
Total n=a+b+c+d			

*Critical value (crit) used to dichotomize the score.

The difference of $p_T - p_R$ is estimated by the quantity $(b - c)/n$.

Based on McNemar’s test, the 95% upper confidence limit (UCL_M) for the quantity $p_T - p_R$ was calculated as

$$UCB_M = \frac{(b - c)}{n} + \frac{1}{n} + 1.645 \sqrt{\frac{(b + c) - \frac{(b - c)^2}{n}}{n}}$$

For any given non-inferiority bound δ , the null hypothesis H_0 may be rejected if the 95% UCB for the quantity $p_T - p_R$ is less than or equal to δ , that is $UCB \leq \delta$. Rejection of the null hypothesis, H_0 , supports the conclusion of non-inferiority of the Test to the Reference.

3.5 Results and Conclusions

3.5.1 Applicant's Analysis Results

Adhesion Study (ESTN/2018/1607)

Table 10 shows the number and proportion of each adhesion score at each evaluation time point and across all time points by treatment group.

The applicant's analysis results for the primary endpoint for adhesion are summarized in Table 11. The upper limit of the 90% confidence interval (upper 95% confidence bound) for the difference in test minus reference least-squares means on the Mean Adhesion Scores (MAS) was less than the non-inferiority (NI) margin of 0.15 ($\delta = 0.15$). Therefore, the applicant concluded that the adhesive properties of Amneal Pharmaceuticals LLC' Norelgestromin and Ethinyl estradiol Transdermal System, 150/35 mcg per day are non-inferior to those of Xulane[®] (norelgestromin and ethinyl estradiol transdermal system) 150/35 mcg per day.

Table 10. Applicant’s Frequency Table of Adhesion Scores at Each Time Point by Treatment

Time	Treatment T Adhesion Score (N=80)						Treatment R Adhesion Score (N=82)					
	0	1	2	3	4	Mean*	0	1	2	3	4	Mean*
0.00 hour	80 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000	82 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000
24.00 hours	80 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000	82 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000
48.00 hours	80 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000	82 (100.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.000
72.00 hours	78 (97.50%)	1 (1.25%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	0.038	81 (98.78%)	1 (1.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.012
96.00 hours	78 (97.50%)	1 (1.25%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	0.038	79 (96.34%)	3 (3.66%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.037
120.00 hours	77 (96.25%)	2 (2.50%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	0.050	71 (86.59%)	11 (13.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.134
144.00 hours	76 (95.00%)	3 (3.75%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	0.063	63 (76.83%)	19 (23.17%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.232
168.00 hours	75 (93.75%)	4 (5.00%)	1 (1.25%)	0 (0.00%)	0 (0.00%)	0.075	60 (73.17%)	22 (26.83%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.268
All**	624 (97.50%)	11 (1.72%)	5 (0.78%)	0 (0.00%)	0 (0.00%)	0.033	600 (91.46%)	56 (8.54%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.085

Source: Applicant’s Study report GCPAMN002 Table 14.2.1.5

* Mean = The sum of scores at the time point / The number of subjects at the time point

** All is the total sum of 0.00 hour, 24.00 hours, 48.00 hours, 72.00 hours, 96.00 hours, 120.00 hours, 144.00 hours, and 168.00 hours

Table 11. Applicant’s Non-Inferiority Analysis Result for Mean Adhesion Scores between Treatments

Mean Adhesion Scores /	Treatment T (N=80)	Treatment R (N=82)	Test minus Reference	P Value*	The 90% CI for the Test minus
LS mean	0.0369	0.0987	-0.0619	0.0423	(-0.1117, -0.0120)
mean (SD)	0.0375 (0.1857)	0.0976 (0.1780)			
median (min, max)	0.0000 (0.0000, 1.4286)	0.0000 (0.0000, 0.7143)			

* Results of the statistical evaluation by ANOVA ($\alpha=0.05$) for the hypothesis of equal treatment effects.

Source: Applicant’s Study report GCPAMN002 Table 11.4-5

Table 12 shows that one (1.25%) patch from the Test group and none (0%) from the Reference group had an adhesion score ≥ 2 at any time point. Table 14 shows that adhesion score 2 occurred at Hour 72 for this Test subject. Table 13 reports that one (1.27%) subject had the Test mean adhesion score greater than the corresponding Reference mean adhesion score by 1 or more. No subjects had the Reference mean adhesion score greater than the corresponding Test mean adhesion score by 1 or more.

Table 12. Applicant’s Proportion of subjects with An Adhesion Score ≥ 2 at Any Time Point between Treatments

Adhesion Score/ Status	Treatment T (N=80)	Treatment R (N=82)
≥ 2	1 (1.25%)	0 (0.00%)

Source: Applicant’s Study report GCPAMN002 Table 14.2.1.2

Table 13. Applicant’s Proportion of Subjects with Test Product Mean Adhesion Score Greater Reference Product by 1 or More, Compared to Proportion of Subjects with Reference Product Mean Adhesion Score Greater Than Test Product by 1 or More

Variable	Status
Test mean adhesion score greater than Reference mean adhesion score by 1 or more (N=79)	1 (1.27%)
Reference mean adhesion score greater than Test mean adhesion score by 1 or more (N=79)	0 (0.00%)

Source: Applicant’s Study report GCPAMN002 Table 14.2.1.3

Table 14. Applicant’s Time to an Adhesion Score ≥ 2 between Treatments

Variables/ Status	Treatment T (N=80)	Treatment R (N=82)
Adhesion Score ≥ 2		
Total Number	80	82
Event number (%)	1 (1.25%)	0 (0.00%)
mean time (hrs)	72	NA
median time (hrs)	72	NA
95% CI of median (hrs)	NA	NA

Source: Applicant’s Study report GCPAMN002 Table 14.2.1.4

Irritation/Sensitization Study GCPAMN002

Irritation Analysis:

The applicant’s analysis of MIS is presented in Table 15. For the MIS in the PPPI, the mean difference between the Test and Reference groups was 0 and the corresponding 90% upper confidence bound (UCB) was 0.001, which is less than the NI margin for irritation 0.20. Therefore, the applicant concluded that the Test patch/system was non-inferior to the Reference patch/system.

Table 15. Applicant’s Analysis of Mean Irritation Score (Per-Protocol Population for Irritation)

Statistic	Test (N=211)	Reference (N=211)
n	211	211
Mean (SD)	0.016 (0.085)	0.021 (0.098)
Median (Min, Max)	0.000 (0, 0.67)	0.000 (0, 0.67)
Mean Difference		0.00
90% UCB		0.001
p-value		0.159

Source: Table 8 in applicant’s clinical report GCPAMN-002

Abbreviations: ANOVA = analysis of variance; max = maximum; min = minimum; MIS = mean irritation score; SD = standard deviation; UCB = upper confidence bound.

Note: N = Number of subjects in analysis population.

An ANOVA model, taking the MIS as dependent variable, ‘Left arm treatment-Right arm treatment’ as sequence, Treatment as main effects along with subject nested in sequence was analyzed. The SAS procedure Proc Mixed was used with alpha=0.1. 90% UCB was derived from the Estimate statement in Proc Mixed with the option lower tailed.

Sensitization Analysis

A summary of sensitization reactions at Challenge Phase is presented for the PPPS in Table 16. During the Challenge Phase, all the 205 (100%) subjects on the Test patch/system and Reference patch/system had a “dermal response” score of “no evidence of irritation” at 72 hours after the removal of the patch. One subject (0.5%) on the Test patch/system and 2 (1.0%) subjects on the

Reference patch/system had a “dermal response” score of “minimal erythema, barely perceptible” at 30 minutes.

All the 205 (100%) subjects on the Test patch/system and Reference patch/system also reported an “other effects” score of “no other observations” at 72 hours after the removal of the patch during the Challenge Phase. Two subjects (1.0%) on the Test patch/system and 3 (1.5%) subjects on the Reference patch/system had an “other effects” score of “slightly glazed appearance” at 30 minutes, while 1 subject (0.5%) on the Reference patch/system had an “other effects” score of “marked glazed appearance” at 30 minutes.

Table 16. Applicant’s Summary of Sensitization Reactions at Challenge Phase (Per-Protocol Population for Sensitization)

	Test (N=205)				Reference (N=205)			
	30 mins	24h	48h	72h	30 mins	24h	48h	72h
Dermal Response Score								
No evidence of irritation	204 (99.5)	195 (95.1)	196 (95.6)	205 (100)	203 (99.0)	195 (95.1)	196 (95.6)	205 (100)
Minimal erythema, barely perceptible	1 (0.5)	0	0	0	2 (1.0)	0	0	0
Definite erythema, readily visible; or minimal edema; or minimal papular response	0	0	0	0	0	0	0	0
Erythema and papules	0	0	0	0	0	0	0	0
Definite edema	0	0	0	0	0	0	0	0
Erythema, edema, and papules	0	0	0	0	0	0	0	0
Vesicular eruption	0	0	0	0	0	0	0	0
Strong reaction spreading beyond application site	0	0	0	0	0	0	0	0
Other Effects Score								
No other observations	203 (99.0)	195 (95.1)	196 (95.6)	205 (100)	201 (98.0)	195 (95.1)	196 (95.6)	205 (100)
Slightly glazed appearance	2 (1.0)	0	0	0	3 (1.5)	0	0	0
Marked glazed appearance	0	0	0	0	1 (0.5)	0	0	0
Glazing with peeling and cracking	0	0	0	0	0	0	0	0
Glazing with fissures	0	0	0	0	0	0	0	0
Film of dried serous exudates covering all or part of the patch site	0	0	0	0	0	0	0	0
Small petechial erosions and/or scabs	0	0	0	0	0	0	0	0

Source: Applicant’s clinical report GCPAMN-002 Table 14.2.1.2.1

Note: N = Number of subjects in analysis population. Percentages were calculated using the corresponding column header count.

3.5.2. FDA Reviewer’s Results

Adhesion Analysis (ESTN/2018/1607)

Table 17. FDA’s Analysis for the Mean Adhesion Scores using Mixed Model (PPPA) (N=83)

Test N=80 LS Mean μ_T (SD)	Reference N=82 LS Mean μ_R (SD)	LS Mean Difference $\mu_T - \mu_R$	95% UCB for LS Mean Difference $\mu_T - \mu_R$	Pass the Non- inferiority test
0.03681 (0.01964)	0.09353 (0.01942)	-0.05672	-0.01160	Pass

Source: Reviewer’s Analysis

FDA’s analysis for the primary endpoint mean adhesion score among PPPA is reported in Table 17. It is shown that the 95% upper confidence bound (UCB) for mean difference between the Test and Reference mean adhesion score ($\mu_T - \mu_R$) was -0.01160, which is less than the non-inferiority margin for adhesion 0.15. Therefore, the non-inferiority of the Test product to the Reference product is demonstrated with regard to the primary endpoint using PPPA.

FDA’s analysis results on other endpoints are reported in Tables 18 and 19, which agree with the applicant’s analyses in Tables 12 and 13. For the time to an adhesion score ≥ 2 compared between T and R, if there were a sufficient number of events, a Kaplan Meier cumulative incidence could be plotted. However, only one Test patch had adhesion score ≥ 2 at Hour 72, therefore, no Kaplan Meier plot was drawn.

Table 18. FDA’s Proportion of Subjects with an Adhesion Score ≥ 2 at Any Time Point

Proportion of subjects with an adhesion score ≥ 2 at any time point in Product T	Proportion of subjects with an adhesion score ≥ 2 at any time point in Product R
1.25% (1/80)	0% (0/82)

Source: Reviewer’s Analysis

Table 19. FDA’s Proportion of Subjects with MAS Difference of 1 or More for PPPA

Proportion of subjects with T mean adhesion score – R mean adhesion score ≥ 1	Proportion of subjects with R mean adhesion score – T mean adhesion score ≥ 1
1.27% (1/79)	0.0% (0/79)

Source: Reviewer’s Analysis

Irritation Study (GCPAMN002)

Table 20 presents FDA’s descriptive statistics of the mean irritation scores for the PPPI for the Test and Reference products.

Table 20. FDA’s Descriptive Statistics for Mean Irritation Scores for PPPI (N=211)

Mean Irritation Scores (Combined: Dermal Response + Other Effects)	Test Product	Reference Product
N	211	211
Mean (Standard Deviation)	0.0158 (0.0846)	0.0205 (0.0981)
Median (Range)	0 (0 – 0.667)	0(0 –0.667)

Source: Reviewer’s Analysis

Table 21 presents FDA’s frequency of the combined irritation score (based on the dermal response and other effects scores) for the Test and Reference at each measurement and across all time points as well as the mean irritation score on Day 8,15, and 22 and overall in the Induction Phase. Zero (0) subject had a combined “dermal response” and “other effects” irritation scores of 3 or more for each product.

Table 21. FDA’s Number and Frequency (%) of Combined Irritation Score (PPPI, N=211)

Product	Visit Day	Combined “Dermal Response” and “Other Effects” Scores						
		0	1	2	3	4	5	Mean
Test	8	210 (99.53)	1 (0.47)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0047
	15	210 (99.53)	1 (0.47)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0047
	22	205 (97.16)	4 (1.90)	2 (0.95)	0 (0.0)	0 (0.0)	0 (0.0)	0.0379
	All	625 (99.20)	6 (0.95)	2 (0.32)	0 (0.0)	0 (0.0)	0 (0.0)	0.0159
Reference	8	208 (98.58)	3 (1.42)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0142
	15	209 (99.05)	2 (0.95)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0095
	22	206 (97.63)	2 (0.95)	3 (1.42)	0 (0.0)	0 (0.0)	0 (0.0)	0.0379
	All	623 (98.89)	7 (1.11)	3 (0.48)	0 (0.0)	0 (0.0)	0 (0.0)	0.0206

Source: Reviewer’s Analysis

FDA’s non-inferiority analyses based on the mean irritation scores among PPPI showed that the 95% upper confidence bound (UCB) for the adjusted mean difference between the Test and Reference Group ($\mu_T - \mu_R$) was 0.0031 (Table 22), which was less than the NI margin for irritation 0.2. Therefore, the irritation potential of the Test product was no worse than that of the Reference product.

Table 22. FDA’s Analysis for the Mean Irritation Scores Using Mixed Model (PPPI) (N=211)

Test (LS Mean μ_T) (SD)	Reference (LS Mean μ_R) (SD)	Adjusted LS Mean Difference $\mu_T - \mu_R$	95% UCB for Adjusted LS Mean Difference	Pass the Non-inferiority test
0.01580 (0.006318)	0.02052 (0.006318)	-0.00472	0.0031	Yes

Source: Reviewer’s Analysis

In addition to the primary endpoint analysis, no subjects had an irritation score ≥ 3 at any time for TEST or Reference group (Table 23). Based on the 95% UCB for the difference in proportions, the Test can exceed the Reference by at most 0.47 percentage points regarding the proportion of subjects who had cumulative irritation scores greater than or equal to 3.

Table 23. FDA’s Analysis on Proportion of Subjects with an Adhesion Score ≥ 2 at Any Time Point (PPPI) (N=211)

Test Score ≥ 3 at any time point	Reference Score ≥ 3 at any time point	$p_T - p_R^*$	95% UCL# for $p_T - p_R$
0	0	0	0.0047

* p_T = irritation score ≥ 3 for Test and p_R = irritation score ≥ 3 for Reference.

Source: Reviewer’s Analysis

Sensitization (Study GCPAMN002)

Table 24 presents the frequency of irritation scores in the Challenge period for the Per-Protocol population for Sensitization (PPPS).

Table 24. FDA’s Frequency of irritation scores for the Challenge period (PPPS)

Evaluation Time	Product	Combined Irritation score					
		0	1	2	3	4	5
30 min	Test	204 (99.51)	1 (0.49)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Reference	202 (98.54)	3 (1.46)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
24 hours	Test	195 (95.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Reference	195 (95.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
48 hours	Test	196 (95.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Reference	196 (95.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
72 hours	Test	202 (98.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Reference	202 (98.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Reviewer’s Analysis

According to FDA’s guidance, subjects will have been considered to have demonstrated a potential sensitization response for a specific patch by the irritation rating scales if the following criteria are met:

1. The subject has at least one irritation assessment occurring at more than 24 hours (i.e., at 48 or 72 hours) after the removal of the challenge phase patch.
2. The subject has an Irritation Score (“dermal response” + “other effects”) that is 2 or more at the last evaluation during the challenge phase.
3. The above two criteria were met during both the challenge phase and the re-challenge phase, if the subject completed a re-challenge phase.

Zero (0) subject in the PPPS had an irritation score of 2 or higher for the Test Patch or Reference Patch at any time point in the Challenge phase. Therefore, no subject demonstrated a potential sensitization reaction to both Test and Reference patches in the Challenge Phase.

4 SUMMARY AND CONCLUSIONS

4.1 Side by Side Tables for DCR Reviewers

The applicant's and the reviewer's analysis results on Adhesion and Irritation studies are shown side-by-side in Table 25 and Table 26.

Table 25. Adhesion Analysis Results (Mean Adhesion Score) for PPPA by Applicant and FDA

	Applicant*	FDA
LS Mean Test (N=80)	0.0369	0.03681
LS Mean Reference (N=82)	0.0987	0.09353
LS Mean Difference $\mu_T - \mu_R$	-0.0619	-0.05672
95% UCB for LS Mean Difference $\mu_T - \mu_R$	-0.0120	-0.01160
Pass the Non-inferiority test	Yes	Yes

*Source: Applicant's Clinical report amendment for ESTN/2018/1607 Table 11.4-5

Table 26. Irritation Analysis Results (Mean Irritation Score) for PPPI by Applicant and FDA

	Applicant*	FDA
LS Mean Test (N=211)	0.016	0.0158
LS Mean Reference (N=211)	0.021	0.0205
LS Mean Difference $\mu_T - \mu_R$	0.0**	-0.00472
95% UCB for LS Mean Difference $\mu_T - \mu_R$	0.001 ^a	0.0031
Pass the Non-inferiority test	Yes	Yes

*Source: Applicant's Clinical report amendment for GCPAMN002 Table 8

** not correct (from applicant's report)

a 90%UCB

4.2 Statistical Issue and Findings

Adhesion Study ESTN/2018/1607

The primary endpoint (mean adhesion scores) was analyzed using a mixed linear model after incorporating the cohort effect. Data from 83 subjects (80 Test patches and 82 Reference patches) were included in the primary analyses utilizing the PPPA. The 95% upper confidence bound (UCB) for the difference of the T and R mean adhesion score ($\mu_T - \mu_R$) was -0.01106, which is less than the non-inferiority margin for adhesion: 0.15. Therefore, the non-inferiority of the Test product to the Reference product was demonstrated regarding the primary endpoint mean adhesion score using PPPA in the Adhesion Study ESTN/2018/1607.

Irritation and Sensitization Study GCAPMN002

Irritation

The primary endpoint (mean irritation score) was analyzed using a mixed linear model. The non-inferiority analyses based on the mean irritation scores showed that the one-sided 95% upper confidence bound (UCB) for the difference of the T and R mean adhesion score ($\mu_T - \mu_R$) was 0.0031, which was less than the non-inferiority margin for irritation: 0.2. Therefore, non-inferiority was established for the Test patch versus the Reference patch in the primary endpoint mean irritation score using PPPI in the Irritation and Sensitization Study GCAPMN002.

Sensitization

In the Challenge Phase, no subjects from either treatment groups demonstrated a potential sensitization reaction to the Reference patch or Test patch. Therefore, non-inferiority was established for the Test patch versus the Reference patch in sensitization potential using PPPS in the Irritation and Sensitization Study GCAPMN002.

No major statistical issues were identified in this ANDA application.

4.3 Conclusions

The Test patch was found to be non-inferior to the Reference patch for irritation, sensitization, and adhesion.

Skin Irritation: The non-inferiority of the Test versus the Reference product was established using the mean combined irritation scores from the Induction Phase of the Irritation/Sensitization study GCPAMN002.

The statistical review and evaluation of the data submitted for ANDA 213950 Irritation/Sensitization Study GCPAMN002 support approval for irritation.

Skin Sensitization: The Test product was shown to be no more sensitizing than the Reference product using the proportion of potential sensitization from the Challenge Phase of the Irritation/Sensitization study GCPAMN002.

The statistical review and evaluation of the data submitted for ANDA 213950 Irritation/Sensitization Study GCPAMN002 support approval for sensitization.

Patch Adhesion: Non-inferiority of the Test versus the Reference product was established using the mean adhesion scores from the Adhesion study ESTN/2018/1607. The statistical review and evaluation of the data submitted for ANDA 213950 Adhesion Study ESTN/2018/1607 support approval for adhesion.

4.4 Comments to be Sent to the Applicant by the Regulatory Project Manager

Table 27. Justification of Major Deficiency Designation

Deficiency Classification	☐ Major ☐ Minor ☒ Not Applicable
Deficiency Theme	☐ New Studies Needed ☐ Inconsistent Information ☐ Unresolved Statistical Issues ☐ Other
Deficiency Description	N/A
Justification for Major Deficiency Designation	N/A

The data of adhesion study (adad.xpt) the applicant submitted on 01/29/2020 had no indication flag for Per-protocol population for adhesion (PPPA), and the reason for exclusion from the PPPA.

The data of irritation/sensitization study (adis.xpt) the applicant submitted on 12/18/2019 had no reason for exclusion from the Per-protocol population for irritation (PPPI) and Per-protocol population for sensitization (PPPS).

5 REFERENCES

Draft Guidance on **Ethinyl Estradiol; Norelgestromin**. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), Nov 2019.

Draft Guidance for Industry. Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2018.

Draft Guidance for Industry. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2018.

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). *Statistical Methods for Rates and Proportions* (2nd edition). New York: Wiley-Interscience.

McNemar, Q. (1947). Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*, 12, 153-157.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

OTHER REVIEW(S)

CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product	Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/0.035 mg/day
ANDA# Applicant	ANDA 213950 Amneal Pharmaceuticals LLC
RLD#/Approval Date Applicant	NDA 021180: ORTHO EVRA (ETHINYL ESTRADIOL; NORELGESTROMIN) Transdermal Film, 0.035MG/24HR;0.15MG/24HR; approved on November 20, 2001, JANSSEN PHARMACEUTICALS INC; Note: Current marketing status of RLD product is discontinued.
Reference Standard (RS)	ANDA 200910: XULANE (ETHINYL ESTRADIOL; NORELGESTROMIN) Transdermal Film, 0.035MG/24HR;0.15MG/24HR; Approved on April 16, 2014
Consult Response To	Madhusudana Rao Chaluvadi, Ph.D. Division of Bioequivalence III (DB III), Office of Bioequivalence, Office of Generic Drugs
Reason for Consult	DB III requests DCR's opinion on whether the Applicant's responses in Amendment dated 08/28/2020 are adequate to support that the higher percentage of subjects on the test product having Ethinyl Estradiol (EE) concentrations less than 25 pg/ml at 168 hrs (38.9%, 28 subjects) compared to that of the reference product (16.7%, 12 subjects) and the drop of EE concentrations in Amneal's test product from 72 to 168 hours compared to that of the RS Xulane® pose any safety or efficacy concern.
Materials Reviewed	• Clinical Review of NDA 021180 dated 11/20/2001 • Clinical Pharmacology Review of NDA 021180 dated 11/19/2001 • Bioequivalence Review of ANDA 213950 dated 8/13/2020 • DCR's Comparative Analyses Review dated 3/18/2020 • Documents submitted by Applicant in sequence 0012 (dated 8/28/2020) in Response to Complete Response Letter • RLD Drug Product Label dated 8/2017 • Product Specific Guidance on Norelgestromin and Ethinyl Estradiol Transdermal System; Recommended 5/2009, revised 11/2019
Primary Reviewer	María del C. Ríos, MD, MPH Physician
Secondary Reviewer	Carol Kim, Pharm.D. Team Leader, ANDA Team I
Tertiary Reviewer	Kachikwu Illoh, MD Division Director
Date of Submission	8/28/2020
Date Consult Received	9/11/2020
Date of Completion	12/14/2020
GDUFA	2/27/2021
Conclusion	DCR concludes that the information provided by the Applicant on 8/28/2020 is adequate, and the differences in EE concentrations less than 25 pg/mL from 72 hours to 168 hours (at time of patch removal) observed in a single dose PK study pose no safety or efficacy concern from a clinical perspective.

1 Executive Summary:

Amneal Pharmaceuticals LLC (Applicant) submitted ANDA 213950 for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg /0.035 mg/day on 10/16/2019. The reference listed drug (RLD) is Ortho Evra (Ethinyl estradiol; Norelgestromin) Transdermal Film, 0.035MG/24HR;0.15MG/24HR (NDA 021180), approved on 11/20/2001. Ortho Evra was discontinued in 2014. There is a Federal Register determination stating that the product was not discontinued or withdrawn for safety or efficacy reasons. The reference standard (RS) is Xulane (Ethinyl estradiol; Norelgestromin) Transdermal Film, 0.035MG/24HR;0.15MG/24HR (ANDA 200910), approved on 4/16/2014.

This review is the Division of Clinical Review (DCR)'s response to the consult request from Dr. Madhusudana Rao Chaluvadi, Ph.D., in the Division of Bioequivalence (DB) III, Office of Bioequivalence¹ dated 9/11/2020. DB III observed greater number of individual subjects having lower than 25 pg/mL concentrations of ethinyl estradiol receiving the proposed Amneal's product at 168 hours compared to those receiving Xulane [28 subjects (38.9%) in test vs. 12 subjects (16.7%) in Xulane] in a fasting bioequivalence (BE) study (ESTN/2018/1607). On 8/16/2020, DB III sent the following bioequivalence deficiency comments to the Applicant in a Complete Response Letter (CRL)² related to this consult request:

“After reviewing your submitted justifications in the amendment dated June 12, 2020, we still have concerns on the significant lower concentration of ethinyl estradiol (EE) in your test product at 168 hours compared to Xulane® in your pivotal fasting BE study (No. ESTN/2018/1607). We acknowledge that based on the inclusion of data from 72 subjects in the pharmacokinetic and statistical analyses, the mean concentration for the test product (i.e., 29.5 pg/ml) at 168 hours is within the C_{ss} target range of 25-75 pg/ml of EE for optimum efficacy identified by the innovator of the reference listed drug, Ortho Evra®. However, the data show that the EE concentrations for 38.9% (28 subjects) of the total subjects at 168 hours were lower than 25 pg/ml for the test product, compared to 16.7% (12 subjects) of the total subjects for the reference product. This difference in EE concentration between the test and reference products may lead to subjects experiencing sub-therapeutic EE levels. The agency requests that you provide an explanation along with supportive information for why the difference in EE concentrations is not expected to have an impact on the safety or efficacy of the drug product.”

On 8/28/2020, the Applicant provided a response³ to the CRL. DB III is requesting DCR's input on the following three questions regarding the Applicant's response to the CRL:

1. Are Amneal's justifications provided in 08/28/2020 amendment sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, i.e. at the time of patch removal is not expected to have an impact on the safety or efficacy of the drug product?
2. Is there any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal's test product from 72 to 168 hours comparing to RS Xulane®?

¹ ANDA 213950 Consult Request to DCR by Madhusudana Rao Chaluvadi, Ph.D, dated 9/11/2020, uploaded in GDRP: <https://panorama.fda.gov/document/view?ID=5f598673001ba34a1636bad27fb0f54d>

² ANDA 213950 Complete Response Letter, dated 8/16/2020, uploaded in GDRP: <https://panorama.fda.gov/document/view?ID=5f35d3fb009872773c71f8b2ea6759b8>

³ [\\CDSESUB1\evsprod\anda213950\0012\m1\us\1-2-cover-letter-esignd-seq-0012-20200828.pdf](https://CDSESUB1\evsprod\anda213950\0012\m1\us\1-2-cover-letter-esignd-seq-0012-20200828.pdf)

3. If the answer is ‘yes’, to the above questions, we seek your advice on whether PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product?

DCR concludes that Amneal’s justifications provided in Amendment-12 dated 08/28/2020 are adequate. After reviewing the information provided by the Applicant in their response to the CRL in Amendment-12, no safety or efficacy concerns were noted. As recommended by the Product Specific Guidance (PSG) of this product, the Applicant’s study met BE criteria and demonstrated that the test product is bioequivalent to the RS. The test formulation was deemed acceptable with a minimal difference in inactive ingredients. Although higher proportion of subjects in the test product had individual EE concentrations below 25 pg/mL at the patch removal (168 hours), the mean C_{ss} of EE concentrations remained above the targeted efficacy threshold of 25 pg/mL at 168 hours. Some individual patients in an NDA study following a single patch application (Figure 2 below) had C_{ss} EE concentrations below the target range. Thus, the difference in proportion of subjects having individual EE concentrations below the target range between the test product and the RS may not be considered clinically meaningful when the mean EE concentration at 168 hours was above the target range of 25 pg/mL.

Based on DCR assessment, the decrease in EE concentration from 72 hours to 168 hours, which appears to be comparable between products, do not pose a safety or efficacy concern from a clinical perspective.

From DCR’s perspective, the difference in proportion of subjects with EE concentrations less than 25 pg/mL at 168 hour is not a safety or efficacy concern to require a minimum concentration of EE level at the time of patch removal (i.e., 168 hour) for this drug product, and the drop in EE concentrations in Amneal’s test product from 72 hours to 168 hours (at time of patch removal) observed in a single dose PK study poses no safety or efficacy concern from a clinical perspective.

2 Background

Amneal submitted ANDA 213950 on 10/16/2019. In support of their application, the Applicant submitted a single-dose, two-way crossover bioequivalence with pharmacokinetic endpoints study (ESTN/2018/1607) comparing its test product, Norelgestromin and Ethinyl estradiol, 0.15 mg/0.035 mg/day to the reference standard (RS), Mylan’s Xulane® (ANDA 200910), both applied at abdominal site for 7 days, to demonstrate BE. According to DB III, the 90% CIs for AUCs and C_{max} for both EE and NGMN (norelgestromin) met the acceptable BE criteria of 80.00-125.00%.⁴ Amneal’s test formulation contains 0.289 mg loading dose of EE, which is 54.5% of the loading dose in the RS, Xulane® (0.53 mg) and 38.5% of EE loaded in the RLD, Ortho Evra® (0.75 mg), NDA 021180.

Per DB III’s assessment of the mean concentration vs. time profiles, there is a rapid decrease of EE concentration in Amneal’s test product (compared to the reference product, Xulane®) after 72 hrs and until 168 hours. In addition, there is a higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hours (time of patch removal). The NDA review for the

⁴ A213950N000DB-Review01-12182019.docx (<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

RLD indicates that the NDA sponsor identified steady state concentrations within the target range of 25-75 pg/mL for EE, along with 0.6-1.2 ng/mL for Norelgestromin, for optimum drug efficacy⁵.

On 08/16/2020, FDA sent a Complete Response (CR) Letter to the Applicant requesting them to provide an explanation along with supportive information for why the difference in EE concentrations between the test and reference products at 168 hours is not expected to have an impact on the safety or efficacy of the drug product. On 08/28/2020, the Applicant submitted its post CR amendment with their response to the deficiency. On 9/11/2020, DB III sent a consult to DCR which can be found at:

<https://panorama.fda.gov/document/view?ID=5f598673001ba34a1636bad27fb0f54d>

On 10/8/2020, the Applicant submitted Reconsideration Teleconference Request.

On 10/26/2020, OGD had a meeting with the Applicant. The Applicant provided some new information at the Reconsideration Teleconference Request meeting dated 10/26/2020. The Applicant stated that the safety and efficacy of the test product's EE concentrations were supported by the EE concentration profiles noted from other marketed products such as NuvaRing, which has lower EE concentrations than Amneal's product with similar efficacy. Since the nature of the question is in comparison to the RLD and RS and not a generalized question related to EE concentrations of other similar drug products, the information from NuvaRing was not considered in this consult response.

3 Regulatory Background

3.1 Other ANDA Applications

As of 11/9/2020, there are 2 ANDAs pending review for this RLD/RS as follows:

- ✓ ANDA 214594, submitted by Zydus Noveltch Inc. on 4/3/2020, has not been reviewed by DCR.
- ✓ ANDA 213977 submitted by Teva Pharmaceuticals on 10/16/2019
A Comparative Analyses Review was completed by DCR on 6/4/2020 with an acceptable outcome (minor design differences)

3.2 Orange Book

According to the Orange Book search on 11/4/2020, the RLD, Ortho Evra (NDA 21180), was discontinued, and the RS, Xulane (ANDA 200910), is the only approved generic drug product for Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg /0.035 mg/day as shown below.

⁵ DARRTS, NDA 021180, CHATTERJEE, DHRUBA J, 11/19/2001, REVCLINPHARM-01(General Review) page 18/41:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8016757a&_afRedirect=323997919332409

Mkt. Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ETHINYL ESTRADIOL; NORELGESTROMIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR			RS	MYLAN TECHNOLOGIES INC
DISC	ETHINYL ESTRADIOL; NORELGESTROMIN	ORTHO EVRA	N021180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24HR; 0.15MG/24HR **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		RLD		JANSSEN PHARMACEUTICALS INC

3.3 Controlled Correspondence Relevant to this Review

As of 11/4/2020, the Applicant has submitted six controlled correspondence (CC) to the Office of Generic Drugs (OGD). The following CCs are relevant to this consult:

- CC 9045249** – Submitted by Amneal Pharmaceuticals on 7/11/2016, requesting revisions to PSG.
FDA Response (7/11/2016): “Your submission will be forwarded to the appropriate review discipline for substantive review and response.” FDA’s first draft on updated PSG dated 8/19/2016.
- CC 10376677** – Submitted by Amneal Pharmaceuticals on 9/26/2016. The Applicant notes that the PSG recommends that a PK study is conducted using 0.02mg/24 hr; 0.15mg/24 hr strength patch and a skin irritation and sensitization study is to be conducted using 0.02 mg/24 hr; 0.15 mg/24 hr (Dose: One-half of a 0.02 mg/24 hr; 0.15 mg/24 hr patch). The product strength is incorrect as the strength for NDA # 21180 is 0.035mg/24 hr; 0.15mg/24 hr.
FDA Response (10/12/2016): “Please note the RLD link for ethinyl estradiol; norelgestromin transdermal extended release film has been updated on the Product-Specific Recommendations for Generic Drugs website”.
- CC 21822019** – Submitted by Amneal Pharmaceuticals on 3/22/2018. The Applicant submitted a Statistical Analysis Plan (SAP) for their adhesion study (Protocol # 16-VIN-0236).
FDA Response (3/26/2018): “Your submission will be forwarded to the appropriate review discipline for substantive review and response.” Re-assigned Protocol number 21822019.

3.4 Product Specific Guidance (PSG)

The Product Specific Guidance for Ethinyl estradiol; Norelgestromin; transdermal extended release film can be found at:

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

Three studies are recommended as shown below.

- Type of study: Bioequivalence study with pharmacokinetic endpoints
 Design: Single-dose, two-treatment, two-period crossover in vivo
 Strength: 0.035 mg/24 hr; 0.15 mg/24 hr
 Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
 Additional comments:
 • Unless otherwise justified, the ethinyl estradiol; norelgestromin TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for

dosing in the approved labeling for the reference product, and worn for 7 days.

Applicants should randomize subjects to receive either the test or reference product in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.

2. Type of study: Adhesion study

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 0.035 mg/24 hr; 0.15 mg/24 hr

Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.

3. Type of study: Skin irritation and sensitization study

Design: Randomized, evaluator-blinded, within-subject repeat design, in vivo

Strength: 0.035 mg/24 hr; 0.15 mg/24 hr (Dose: One-half of a 0.035 mg/24 hr; 0.15 mg/24 hr TDS)

Subjects: Healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.

4 Drug Product Label

The current product label for Ortho Evra (Ethinyl estradiol; Norelgestromin) Transdermal Film⁶, 0.035MG/24HR;0.15MG/24HR (NDA 021180 S-048) is dated 8/9/2017. Specific sections of the most recent RLD label which are relevant to this review are as follows:

Boxed Warning:

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, and PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL.
See full prescribing information for complete boxed warning.

Women over 35 years old who smoke should not use ORTHO EVRA. (4)

Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptives (CHC) use. (4)

There may be an increased risk of venous thromboembolism (VTE) among women who use the ORTHO EVRA patch compared to women who use certain oral contraceptives. (5.1)

The pharmacokinetic (PK) profile of ethinyl estradiol (EE) for the ORTHO EVRA patch is different from the PK profile for oral contraceptives in that it has higher area under the time-concentration curve, steady state concentrations and lower peak concentrations. (5.2)

Indications	ORTHO EVRA is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch. <u>Limitation of Use:</u> ORTHO EVRA may be less effective in preventing pregnancy in women weighing 198 lbs (90 kg) or more.
Contraindications	• A high risk of arterial or venous thrombotic diseases • Breast cancer or other estrogen- or progestin-sensitive cancer • Liver tumors or liver disease • Undiagnosed abnormal uterine bleeding • Pregnancy

⁶ RLD Drug Product Label: Ortho Evra (Ethinyl estradiol; Norelgestromin) Transdermal Film, accessed at Drug@FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s048lbl.pdf

	• Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir
Significant Warnings and Precautions	• Vascular risks: Stop ORTHO EVRA if a thrombotic event occurs. Stop 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. • Liver disease: Discontinue ORTHO EVRA if jaundice occurs. • High blood pressure: Do not prescribe ORTHO EVRA for women with uncontrolled hypertension or hypertension with vascular disease. • Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking ORTHO EVRA. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. • Headache: Evaluate significant change in headaches and discontinue ORTHO EVRA if indicated. • Uterine bleeding: Evaluate irregular bleeding or amenorrhea.
Dosing and Administration	• ORTHO EVRA uses a 28-day (four-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for three weeks (21 total days). Week Four is patch-free. • Apply each new patch on the same day of the week. Wear only one patch at a time. • Do not cut or alter the patch in any way.

Reviewer’s Comments:

- *The Applicant submitted a pharmacokinetic bioequivalence study (ESTN/2018/1607), a randomized, two-treatment, two-sequence, two-period, single application, two-way crossover study, in 84 healthy, non-pregnant, non-lactating female subjects. The study design was deemed adequate by the DB III, and the study design is consistent with the recommendations in the PSG.*
- *The adherence component of study ESTN/2018/1607 was deemed acceptable by DCR on 6/19/2020⁷.*

5 Summary of RLD studies relevant to consult request

- **RLD Studies:** The safety and efficacy evaluation for the RLD, Ortho Evra was based on the information on 10 clinical pharmacology studies. As per the Clinical Pharmacology review of NDA 021180⁸, a C_{ss} range of 0.6 – 1.2 ng/mL for 17d-NGM and 25 – 75 pg/mL of EE for optimum reference efficacy were identified by the NDA sponsor. These ranges were considered acceptable. In multiple dose studies, C_{ss} and AUC for norelgestromin and EE were found to increase slightly over time when compared to Week 1 of Cycle 1. For the approval, mean concentrations and pharmacokinetic

⁷ A213950 Clinical Review by Zhuo J. Zhang, MD, PhD on 6/19/2020, uploaded in GDRP:

<https://panorama.fda.gov/document/view?ID=5eccc8ee000e657ae5ccf78d1fa3bfb9>

⁸DARRTS, NDA 021180, CHATTERJEE, DHRUBA J, 11/19/2001, REVCLINPHARM-01(General Review) page 18/41:

https://darrrts.fda.gov//darrrts/faces/ViewDocument?documentId=090140af8016757a&_afRedirect=323997919332409

parameters were evaluated, not individual concentrations. Table 1 shows the Mean EE concentrations following a Single Application of a Transdermal Contraceptive System (Study NRGEEP-PHI-003). Table 2 shows the mean EE concentrations for three cycles randomized to abdomen (#NRGEEP-PHI-013). Table 3 and Figure 1 show the mean EE concentrations for three cycles randomized to buttock (#NRGEEP-PHI-013). Figure 2 shows mean EE steady-state concentrations following a single application at different anatomical sites. Table 4 shows mean EE concentrations at different application sites. Table 5 shows the mean EE concentrations following oral administration of Ortho Tri-cyclen containing 0.035 mg of EE in combination with norelgestromin) for three cycles (#NRGTRI-OC-115).

Table 1: Mean Pharmacokinetic Parameters in Healthy Female Volunteers Following a Single Application of a Transdermal Contraceptive System of 17d-NGM and EE for One Week (Study NRGEEP-PHI-003)

	C ^{ss} ^a (ng/mL)	AUC ₀₋₁₆₈ (ng·h/mL)	AUC ₀₋₂₈₈ (ng·h/mL)	t _{1/2} (h)
17d-NGM				
Mean	0.65	96.0	111	24.5
SD	0.20	31.1	35.2	6.77
% CV	30.0	32.4	31.7	27.6
NG				
Mean	0.68 ^b	89.6	152	39.0
SD	0.34	49.7	86.0	17.2
% CV	50.2	55.4	56.7	44.0
EE				
Mean	38.1 ^c	5749 ^d	6383 ^d	16.8
SD	12.7	1960	2119	4.22
% CV	33.4	34.1	33.2	25.1

^a Average serum concentrations at plateau (48/72-168 h).

^b Steady state not attained; value is mean of all measurable concentrations.

^c pg/mL

^d pg·h/mL

Table 2: Mean (+/-SD) pharmacokinetic parameters in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles: Subjects Randomized to Abdomen (study NRGEEP-PHI-013)

Parameter	Week 1 of Cycle 1	Week 1 of Cycle 3	Week 2 of Cycle 3	Week 3 of Cycle 3
17d-NGM				
t _{max} (h)	72.0 (33.9)	85.2 (37.8)	44.7 (18.7)	45.8 (44.4)
C _{max} (ng/mL)	0.87 (0.44)	1.08 (0.87)	1.17 (0.76)	1.14 (0.52)
C ^{ss} _{48-168h} (ng/mL)	0.65 (0.27)	0.82 (0.56)	0.80 (0.37)	0.81 (0.32)
C _{min} (ng/mL)	0.50 (0.24)	0.67 (0.41)	0.64 (0.27)	0.67 (0.27)
AUC _{0-168h} (ng·h/mL)	102 (40.6)	130 (93.3)	142 (73.2)	141 (59.0)
NG				
t _{max} (h)	147 (49.1)	153 (19.4)	125 (42.2)	85.1 (60.1)
C _{max} (ng/mL)	1.04 (0.73)	1.56 (1.06)	2.70 (1.81)	2.99 (1.70)
C _{avg} (ng/mL)	0.66 (0.36)	1.05 (0.71)	2.18 (1.44)	2.46 (1.27)
C _{min} (ng/mL)	1.03 (0.74)	1.50 (0.97)	2.22 (1.22)	2.28 (1.08)
AUC _{0-168h} (ng·h/mL)	91.5 (59.4)	165 (124)	367 (242)	414 (213)
EE				
t _{max} (h)	101 (39.2)	83.1 (39.3)	68.7 (55.3)	53.5 (39.9)
C _{max} (pg/mL)	74.0 (20.3)	72.6 (23.8)	79.4 (29.2)	95.7 (25.7)
C ^{ss} _{48-168h} (pg/mL)	57.7 (8.64)	56.7 (17.3)	61.6 (19.8)	71.1 (20.4)
C _{min} (pg/mL)	49.5 (9.72)	50.1 (15.5)	54.1 (17.7)	57.4 (18.5)
AUC _{0-168h} (pg·h/mL)	8728 (1495)	8935 (3088)	10407 (3683)	12139 (3241)

Table 3: Mean (+/- SD) Pharmacokinetic Parameters in Healthy Female Volunteers Following Application of a Transdermal Contraceptive System of 17d-NGM and EE for Three Consecutive Cycles: Subjects Randomized to Buttock (study NRGEEP-PHI-013)

Parameter	Week 1 of Cycle 1	Week 1 of Cycle 3	Week 2 of Cycle 3	Week 3 of Cycle 3
17d-NGM				
t_{max} (h)	105 (34.7)	122 (45.1)	41.0 (40.1)	51.0 (41.6)
C_{max} (ng/mL)	0.86 (0.38)	0.89 (0.31)	1.08 (0.42)	0.96 (0.36)
$C^{55}_{48-168h}$ (ng/mL)	0.70 (0.28)	0.70 (0.29)	0.80 (0.23)	0.70 (0.32)
C_{min} (ng/mL)	0.62 (0.27)	0.71 (0.30)	0.57 (0.25)	0.58 (0.32)
AUC_{0-168h} (ng·h/mL)	107 (44.2)	105 (45.5)	132 (57.1)	120 (52.8)
NG				
t_{max} (h)	157 (28.8)	154 (19.0)	115 (53.5)	106 (60.7)
C_{max} (ng/mL)	1.00 (0.30)	1.37 (0.78)	2.34 (1.32)	2.78 (1.50)
C_{avg} (ng/mL)	0.57 (0.15)	0.90 (0.42)	1.88 (1.07)	2.14 (1.22)
C_{min} (ng/mL)	0.94 (0.33)	1.33 (0.76)	1.97 (1.17)	2.07 (1.30)
AUC_{0-168h} (ng·h/mL)	72.4 (20.5)	131 (77.0)	315 (180)	359 (207)
EE				
t_{max} (h)	113 (38.9)	128 (47.3)	49.1 (46.1)	60.0 (59.2)
C_{max} (pg/mL)	56.8 (23.1)	64.3 (20.0)	83.8 (26.5)	78.0 (43.2)
$C^{55}_{48-168h}$ (pg/mL)	46.4 (17.9)	47.6 (17.3)	59.0 (25.1)	49.6 (27.0)
C_{min} (pg/mL)	44.0 (17.9)	54.5 (19.0)	53.6 (24.0)	43.2 (19.0)
AUC_{0-168h} (pg·h/mL)	6796 (2673)	7160 (2893)	10054 (4205)	8840 (5176)

Figure 1: Mean EE Serum Concentrations (ng/mL) in healthy female volunteers following application of ORTHO EVRA on the buttock for three consecutive cycles (NRGEEP-PHI-013).

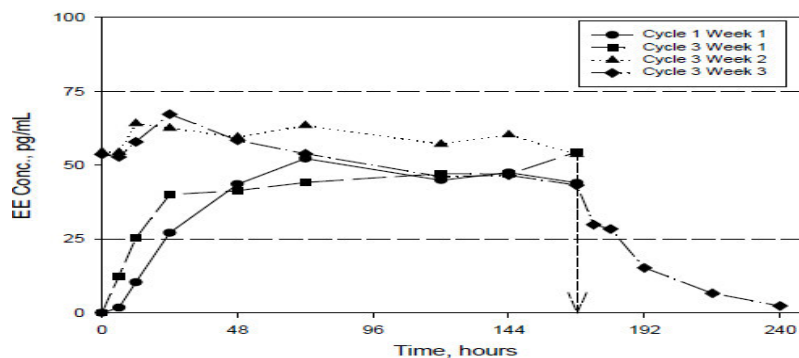
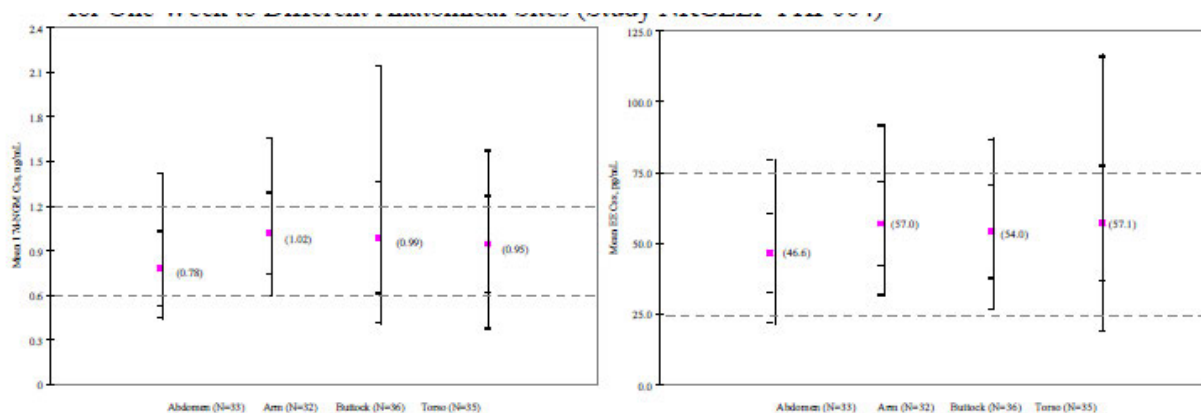


Table 4: Mean (SD) Pharmacokinetic Parameters Obtained from 36 Women Wearing the 20-cm² Seven-Day EVRATM Patch at Different Application Sites (NRGEEP-PHI-004)

Parameter	Abdomen	Arm	Buttock	Torso
17d-NGM				
C _{max} (ng/mL)	0.88 (0.28)	1.18 (0.35)	1.17 (0.50)	1.07 (0.38)
t _{max} (h)	73.5 (32.3)	69.8 (34.1)	78.8 (43.0)	79.6 (42.5)
C ⁵⁵ (ng/mL)	0.78 (0.25)	1.02 (0.27)	0.99 (0.38)	0.95 (0.32)
AUC _{0-168h} (ng·h/mL)	117 (37.6)	155 (44.3)	150 (57.9)	143 (50.4)
AUC _{0-240h} (ng·h/mL)	136 (43.6)	177 (46.4)	174 (64.6)	166 (56.7)
t _{1/2} (h)	27.6 (10.4)	26.1 (6.95)	28.0 (6.90)	30.1 (21.4)
NG				
C _{max} (ng/mL)	1.32 (0.57)	1.71 (0.65)	1.60 (0.69)	1.59 (0.88)
t _{max} (h)	173 (7.85)	170 (19.5)	176 (11.3)	175 (10.3)
C ⁵⁵ (ng/mL)	0.72 (0.31)	0.98 (0.43)	0.86 (0.40)	0.86 (0.50)
AUC _{0-168h} (ng·h/mL)	106 (49.0)	146 (66.9)	131 (65.1)	132 (79.6)
AUC _{0-240h} (ng·h/mL)	169 (73.9)	225 (90.8)	208 (94.7)	208 (117)
t _{1/2} (h)	43.4 (22.3)	45.4 (22.0)	45.1 (17.6)	51.6 (48.1)
EE				
C _{max} (pg/mL)	58.7 (19.9)	69.5 (20.6)	66.3 (23.9)	71.2 (32.2)
t _{max} (h)	56 (27.3)	57.8 (32.7)	52.7 (32.4)	56.2 (26.6)
C ⁵⁵ (pg/mL)	46.6 (14.0)	57.0 (14.9)	54.0 (16.5)	57.1 (20.3)
AUC _{0-168h} (pg·h/mL)	7163 (2211)	8751 (2272)	8391 (2622)	8599 (3161)
AUC _{0-240h} (pg·h/mL)	7766 (2332)	9540 (2437)	9189 (2755)	9523 (3354)
t _{1/2} (h)	16.1 (3.02)	16.4 (3.47)	18.1 (6.43)	17.1 (3.81)

Figure 2: Mean 17d-NGM & EE Steady-State Serum Concentrations vs. Time in Healthy Female Volunteers Following Single Application of a Transdermal Contraceptive System of 17d-NGM and EE for One Week to Different Anatomical Sites (NRGEEP-PHI-004)



[The dashed lines represent the target concentration range; vertical lines represent mean, SD and range of observed values.]

Table 5: Mean (+/-SD) Cmin levels in normal female volunteers following oral administration of Ortho Tri-Cyclen for three cycles (study NRGTRI-OC-115)

	Day 6	Day 7	Day 8	Day 13	Day 14	Day 15	Day 20	Day 21	Day 22
17d-NGM									
Mean	0.30	0.30	0.35	0.34	0.31	0.31	0.45	0.59	0.46
SD	0.09	0.09	0.13	0.09	0.13	0.15	0.13	0.40	0.11
CV %	30.4	28.7	36.3	25.7	41.1	46.6	29.9	67.3	23.5
NG									
Mean	0.99	1.08	1.33	1.88	1.85	1.92	2.33	2.24	2.41
SD	0.47	0.50	0.62	0.66	0.80	0.99	0.67	0.94	0.96
CV %	47.7	46.0	47.1	35.4	43.3	51.5	28.8	41.8	39.8
EE (pg/mL)									
Mean	22.8	21.9	23.9	24.7	21.1	22.0	21.3	31.2	25.4
SD	11.4	10.2	10.2	8.10	8.45	9.20	9.85	26.4	17.6
CV %	49.8	46.7	42.1	32.8	40.1	41.8	46.4	84.4	69.2

Reviewer’s Comments:

- According to the graph shown in Figure 1 above, the mean EE concentrations during the first cycle of patch wear (cycle 1, week 1), show a decrease in EE concentration starting at 72 hours and reach a plateau by 120 hours until 168 hours.

- Per RLD study NRGEEP-PHI-003, following a single dose, the average serum concentrations at plateau (48/72-168h) was 38.1 pg/mL. Per study NRGTRI-OC-115 following oral administration, the mean C_{min} was 21.9 pg/mL on Day 7 and 21.1 pg/mL on Day 14.
- Per RLD label, the EE PK profile for the Ortho Evra patch has a higher C_{ss} and a lower C_{max} compared to oral ethinyl estradiol administration.
- Although the exposure following administration of the patches on the abdomen is higher compared to the other sites such as buttock site, the NDA Clinical Pharmacology reviewer stated that the “mean C_{ss} levels from all anatomic sites are all within the established target range for both the drugs”; the reviewer is referring to mean C_{ss} levels for 17d-NGM and EE. As shown in figure 2 above, some patients showed EE steady-state serum levels below the target range from a single application at abdomen site as well as at torso site.

6 Consult Questions by DB III

Based on the DB III review of study ESTN/2018/1607 in ANDA 213950, DB III noted that the loading amount of EE is lower than that of the RS, but the PK study was acceptable. Per BE review⁹ of ANDA 213950 dated 8/13/2020, the 90% CIs for AUCs and C_{max} for both EE and NGMN met the BE criteria of 80.00-125.00%. After adjusting analysis population, the assessor’s results are as follows:

Ethinyl Estradiol (EE)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1 x 150 µg /35 µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N*	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	6381.51	72	6750.18	72	0.95	90.33	98.95
AUC _∞ (hr *pg/ml)	6459.66	72	6845.92	70**	0.94	90.05	98.87
C _{max} (pg/ml)	46.96	72	46.76	72	1.00	95.91	105.16

* Seven subjects (Nos. (b)(6)) had at least one pre-dose concentration of ethinyl estradiol greater than 5% of their respective C_{max} and were excluded from the PK and statistical analysis.

**Subject (b)(6) were excluded from AUC_i calculation with reference product treatment due to missing the last three and two time-points, respectively and unreliable estimation of elimination rate constant.

Norelgestromin (NGMN)

Norelgestromin and Ethinyl Estradiol Transdermal System, 150 µg /35 µg/day Dose: 1x 150 µg /35µg/day x 7 days Fasting Bioequivalence Study No. ESTN/2018/1607, N=79 completed (Females) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals							
Parameter (units)	Test	N	RLD	N*	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	162429.8	78	160920.3	78	1.01	96.90	105.15
AUC _∞ (hr *pg/ml)	173116.7	78	171855.5	76**	1.01	96.65	104.99
C _{max} (pg/ml)	1029.97	78	1027.76	78	1.00	96.03	104.58

(b)(6) had pre-dose concentration of norelgestromin greater than 5% of C_{max} with reference product treatment and was excluded from the PK and statistical analysis.

(b)(6) were excluded from AUC_i calculation due to missing the last three and two time-points with reference product treatment, respectively and unreliable determination of elimination phase.

⁹ ANDA 213950 Bioequivalence Review by Madhusudana Rao Chaluvadi, Ph.D., dated 8/13/2020, uploaded in GDRP: <https://panorama.fda.gov/document/view?ID=5e9fb87d0009fe06f377c28145f7b422>

Reviewer's Comment:

- The Applicant's study met BE criteria and demonstrated that the test product is BE to the reference product.

DB III stated that the difference in EE concentrations at 168 hours falling below 25 pg/mL was not comparable between the test and the RS. In test group, 38.9% (28 subjects) of EE concentrations were below 25 pg/mL and in Reference group, 16.7% (12 subjects) of EE concentrations were below 25 pg/mL. Thus, DB III was concerned that this difference in EE concentration between the products may lead to subjects experiencing sub-therapeutic EE levels. DB III had the following questions for DCR in their consult request.

Based on the aforementioned information, DBIII is seeking expert opinion from DCR on the following questions:

1. Are Amneal's justifications provided in 08/28/2020 amendment sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, i.e. at the time of patch removal is not expected to have an impact on the safety or efficacy of the drug product?
2. Is there any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal's test product from 72 to 168 hours comparing to RS Xulane®?
3. If the answer is 'yes', to the above questions, we seek your advice on whether PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product?

7 Applicant's Justification dated 8/28/20 in Amendment-12

The main arguments presented by the Applicant are as follows:

- The Applicant questions if the metric "proportion of subjects below 25 pg/mL" is truly related to efficacy. The Applicant proposes to compare the actual range of concentrations observed for both the test and reference instead of the proportion of subjects with EE concentrations below 25 pg/mL. The reference product shows a significant proportion of subjects with EE concentrations below 25 pg/mL at all timepoints. However, the reference product was deemed, safe and efficacious by the FDA.
- The proportion of subjects with a concentration lower than 25 pg/ml is higher for the reference product than for the test product at most timepoints during hours 12 to 168 hours, in PK study (ESTN/2018/1697), submitted in support of ANDA 213950.
- Mean EE concentrations for both test and reference products remained above the efficacy reference level of 25 pg/mL.
- Individual EE concentration levels for the test product did not fall significantly below what was observed with the reference product. In addition, no concentration associated with the test product exceeded the highest reported EE concentration for the reference product. In view of this, the Applicant considers that it is reasonable to expect the test product to have a similar safety profile as the reference product.
- The Applicant states that the test product met bioequivalence criteria to the RS and "the concern raised by the FDA it is not expected to impact efficacy and safety for the consumer and is deemed bioequivalent to the Reference Product".

In support of these arguments, the Applicant included 3 tables in Amendment-12. Table 6¹⁰ shows the proportion of subjects with EE concentrations below 25 pg/mL at each timepoint for the test and reference products. According to the Applicant, at all timepoints, except for 144 and 168 hours, the proportion of subjects with an EE concentration lower than 25 pg/mL is higher for the RS than the test product.

Table 6: Proportions of Subjects Below 25 pg/mL by Collection Time Points

Table 1. Proportion of Subjects Below 25 pg/mL by Collection Time Points

Timepoint (Hours)	# of subjects with concentration < 25 pg/mL (%)		p-value
	Test (N=72)	Reference (N=72)	
12	55 (76.4%)	67 (93.1%)	0.0401
24	28 (38.9%)	41 (56.9%)	0.0284
36	6 (8.33%)	16 (22.2%)	0.0178
48	5 (6.94%)	15 (20.8%)	0.0148
60	4 (5.56%)	6 (8.33%)	0.2051
72	3 (4.17%)	10 (13.9%)	0.0349
84	3 (4.17%)	8 (11.1%)	0.0806
96	4 (5.56%)	10 (13.9%)	0.0611
120	8 (11.1%)	10 (13.9%)	0.1669
144	18 (25%)	9 (12.5%)	0.0349
168	28 (38.9%)	12 (16.7%)	0.0051

Reviewer’s Comment: Based on the information provided by the Applicant in Table 6, EE concentrations were below 25 pg/mL at all time points in the reference group, and except for time points at 144 and 168 hours, the RS had a higher proportion of subjects presenting EE concentrations below 25 pg/mL compared to the test group. Although a higher proportion of subjects in test group had EE concentrations below 25 pg/mL at 144 and 168 hours, the overall extent of absorption (e.g., AUC) based on mean EE concentration was within acceptable BE criteria evidenced by passing 90% CIs (i.e., AUC_t=90.33-98.95; AUC_i=90.05-98.87). Although lower AUC concentrations were observed in the test group compared to the RS, they were shown to be BE per DB III review.

Table 7 below, shows the actual range of EE concentrations between 72 and 168 hours (timepoints), which the Applicant considers more relevant than the proportion of subjects below 25 pg/mL ensuring that the test product does not present concentrations that are significantly below those observed with the reference product.

Table 7: Range of Concentrations Observed at Time Points 72 to 168 Hours

¹⁰ ANDA 213950 Response to Complete Response Letter, dated 8/28/2020, uploaded in DocuBridge: <\\CDSESUB1\evsprod\anda213950\0012\m1\us\1-2-cover-letter-esigned-seq-0012-20200828.pdf> page 3

Table 2. Range of Concentrations Observed at Time Points 72 to 168 Hours

Timepoint (hours)	Mean (Min; Max) (pg/mL)	
	Reference	Test
72	43.61 (14.15; 84.56)	43.91 (17.13; 89.79)
84	46.09 (15.64; 88.72)	44.6 (16.01; 91.13)
96	43.79 (14.52; 85.58)	40.37 (15.89; 79.79)
120	42.26 (15.22; 92.29)	36.36 (15.20; 69.61)
144	41.63 (15.45; 83.91)	32.91 (15.84; 61.11)
168	41.09 (16.46; 87.49)	29.5 (13.95; 50.26)
Range 72 to 168	14.15 to 92.29	13.95 to 91.13

Reviewer’s Comments:

- As shown in Table 7 above, the lowest observed EE concentration associated with the test product in the PK study was 13.95 pg/mL at 168 hour which is very similar to the lowest EE concentration observed for the reference product at 72 hours as 14.15 pg/mL. As noted above in RLD study following a single dose of patch application (Table 1), the steady state averaging serum concentrations, C_{ss}, between 72-168 hours, was 38.1 pg/mL similar to the mean EE concentrations of the test product C_{ss} observed in this PK study from data in Table 7 above (37.94 pg/mL).
- Focusing on the EE concentrations from 72 to 168 hours, concentrations associated with the test product had a higher minimum EE concentration at all time points except at 120 and 168 hours. The mean EE concentration at 120 hours for the test product is 36.36, well within the reference range of 25-75 pg/ml. Although the minimum EE concentration for the test product at 168 hours is 13.95 pg/mL, the mean EE concentration at 168 hours for the test product was 29.5 pg/mL, which is also well within the reference range of 25-75 pg/ml.
- According to figure 2 shown above, some patients’ mean C_{ss} were below the target range following a single patch application of the RLD but for this test product, the mean C_{ss} EE concentrations were all within target range of 25 pg/mL to 75 ug/mL at all time points including at 168 hours.
- Based on the Applicant’s assessments provided in Amendment-12, DCR agrees that EE concentration ranges were comparable between products.
- Based on reviews of NDA studies and PK parameters observed in current PK study against the RS, some subjects had EE concentrations below 25 pg/mL even at C_{ss} with the RLD and the RS. Thus, the difference in proportions of individual EE concentrations below 25 pg/mL at 168 hours between the test and the RS is not a safety or efficacy concern when mean EE concentration at 168 hours was over 25 pg/mL in the test product.

Overall, after reviewing the information provided by the Applicant in their response to the CRL in Amendment-12, no safety or efficacy concerns were noted. As recommended by the PSG of

this product, the Applicant's study met BE criteria and demonstrated that the test product is bioequivalent to the RS. The test formulation was deemed acceptable with a minimal difference in inactive ingredients. Although a higher proportion of subjects in the test product had individual EE concentrations below 25 pg/mL at the time of patch removal (168 hours), the mean C_{ss} of EE concentrations remained above the targeted efficacy threshold of 25 pg/mL at 168 hours. As some individual patients in NDA study following a single patch application had C_{ss} EE concentrations below the target range, the difference in proportion of subjects below the target range between the test product and the RS is not considered clinically meaningful when the mean EE concentration at 168 hours was above the target range of 25 pg/mL.

8 Discussion

To respond to DB III's three consult questions, DCR evaluated the Clinical Pharmacology Review of the RLD (NDA 021180), the Clinical and BE Reviews of ANDA 213950, documents submitted as part of DB III's consult request, RLD Drug Product Label dated 8/2017, PSG on Norelgestromin and Ethinyl Estradiol Transdermal System; Recommended 5/2009, revised 11/2019, and the information provided as part of sequence 0012, dated 8/28/2020 in the Applicant's submission.

Based on the information provided in Amendment-12, DCR agrees with the Applicant that there is no safety or efficacy concern related to reported lower EE concentrations at 168 hours in the test product compared to that in the RS. Thus, for question 3, DCR does not consider that the PSG should be revised based on findings from the current PK study.

DB III's Questions

Question 1:

Are Amneal's justifications provided in 08/28/2020 amendment sufficient to support that higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentration less than 25 pg/ml at 168 hrs, i.e. at the time of patch removal, is not expected to have an impact on the safety or efficacy of the drug product?

Question 2:

Is there any concern from clinical safety/efficacy perspective on the significant drop of EE concentrations in Amneal's test product from 72 to 168 hours comparing to RS Xulane®?

Question 3:

If the answer is "yes", to the above questions, we seek your advice on whether PSG should be revised to include requirement on minimum concentration EE level for individual subjects at the time of patch removal at 168 hrs for this drug product?

DCR's response to Questions 1 and 2:

DCR concludes that Amneal's justifications provided in Amendment-12 dated 08/28/2020 are adequate. Although a higher percentage of subjects for the test product (38.9%, 28 subjects) compared to the reference product (16.7%, 12 subjects) with EE concentrations less than 25 pg/ml at 168 hours (just prior to patch removal) was observed, and the EE concentrations appear to rapidly decrease from 72 to 168 hours in Amneal's product compared to that of Xulane, the

difference in individual subjects' EE concentrations is not expected to have an impact on the safety or efficacy of the drug product for the following reasons:

1. Both the test product and the RS were determined to be bioequivalent based on PK profile comparison in a single dose study (ESTN/2018/1697) by DB III which used mean EE concentrations for determination of BE between products. RS shows higher variability in AUC₀₋₂₄₀ evidenced by higher %CV and wider range compared to the test product, which has maintained the release rate of EE with lesser variability. pAUCs from 0-168 and 72-168 hours between products were shown to be within acceptable BE criteria. Based on the DB III assessment, the proposed test formulation was acceptable.
2. According to the RLD label (Ortho Evra), in one of the clinical studies, the C_{ss} concentrations across all subjects ranged from 23 to 137 pg/mL for EE. Per Clinical Pharmacology review dated 11/19/2001 for the approval of the RLD (NDA 021180), the reviewer noted that the optimum efficacy C_{ss} target concentrations of EE identified by the NDA sponsor was 25-75 pg/mL. However, in one NDA study NRGTRI-OC-115 following oral administration of Ortho Tri-Cyclen for three cycles had the mean C_{min} of EE concentrations observed on Day 7 (i.e., 168 hour) as 21.9 pg/mL and on Day 14 was 21.1 pg/mL, lower than the optimum efficacy concentrations.
3. According to the Applicant's analysis provided in response dated 8/28/20 (see Table 6), up to 93.1% subjects in the reference group had less than 25 pg/mL of EE compared to 76.4% in the test group at 12 hours. At 48 hours (close to C_{max}), up to 20.8% subjects in the reference group had less than 25 pg/mL of EE compared to 6.94% in the test group. Except for 144 and 168 hours, all other time points had significantly higher proportions of subjects who had EE concentrations below 25 pg/mL in the reference group compared to that in the test group.
4. At the time of patch removal (i.e., 168 hours), the mean EE concentration in the test group was 29.5 pg/mL which was above 25 pg/mL and individual EE concentrations ranged from 13.95 to 50.26 pg/mL. In the reference group, the mean EE concentration was 41.09 pg/mL and ranged from 16.46 to 87.49 pg/mL. Based on the Applicant's analysis result, some individual EE concentrations fell below the 25 pg/mL at all time points during the first 7-day patch application within the reference group. The test product had the lowest EE concentration of 13.95 pg/mL at 168 hours compared to 16.46 pg/mL in reference group, but the mean EE concentration was above 25 pg/mL (i.e., 29.5 pg/mL).
5. Per Applicant, EE concentrations ranged from 13.95 to 91.13 pg/mL in the test group compared to 14.15 to 92.29 pg/mL in the reference group from 72 hours to 168 hours. The mean concentrations of EE were comparable between test and reference groups at times 72, 84, 96, 120, and 144 hours. The greatest difference in mean EE concentration between products was at 168 hours (41.09 pg/mL in RS vs. 29.5 pg/mL in test). Considering that the mean of EE concentrations were maintained steady and comparable between products from 72 hours to 144 hours, DCR does not consider that there is a sudden decrease in EE concentrations. Again at 168 hours prior to patch removal, the difference in mean EE concentrations observed is not considered clinically meaningful when the mean EE concentrations in both products were above 25 pg/mL. According to the RLD label, a woman can start using Ortho Evra during the first 24 hours of her menstrual period or on the first Sunday after her menstrual

- period begins. Those who choose to start on the first Sunday after the menstrual period begins are recommended to use a non-hormonal backup method of birth control such as a condom and spermicide or diaphragm and spermicide to prevent unwanted pregnancy for the first 7 days of the first cycle. Therefore, the individual EE concentration differences observed at 168 hours on the first cycle between products do not appear to be a safety or efficacy concern from a clinical perspective since this drug product is indicated for chronic use and users are supposed to have two additional cycles of patch application for a total of 3 cycles every month.
6. Although an optimum range of EE concentrations of 25 pg/mL to 75 pg/mL is noted by the NDA sponsor, DCR is not aware of any other oral or topical patch contraceptives containing EE requiring minimum therapeutic levels, when there is no clear minimum efficacy concentration known for EE in these products.
 7. The RLD studies were evaluated based on mean pharmacokinetic parameters, not individual EE concentrations.

DCR's response to Questions 3:

From DCR's perspective, the difference in proportion of subjects with EE concentrations less than 25 pg/mL at 168 hours does not appear to be a safety or efficacy concern to require a minimum concentration of EE level at the time of patch removal at 168 hours for this drug product.

9 Conclusion

DCR concludes that the information provided by the Applicant on 8/28/2020 is sufficient to support that the observed higher number of subjects in the test group as compared to the reference group with EE concentrations less than 25 pg/mL at time of patch removal (168 hours) and the decrease in EE concentration from 72 hours to 168 hours, which appears to be comparable between products, do not pose a safety or efficacy concern from a clinical perspective.



Maria
Rios

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Kachikwu
Illoh

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**Office of Generic Drugs
DQMM/ORS/OGD CONSULT REVIEW**

To: Madhusudana Rao Chaluvadi, Ph.D., OB/OGD/CDER
Through: April C Braddy, PhD, RAC Acting Director, Division of
Bioequivalence III (DBIII), OB/OGD/CDER
Re: ANDA 213950
Drug Product: Ethinyl Estradiol; Norelgestromin Transdermal Extended Release
Film, 0.035MG/24HR; 0.15MG/24HR
Original Submission: 01/10/2020
Date of Consult Request: 05/18/2020
Date of Review: 07/15/2020
Consultant: Eleftheria Tsakalozou, Ph.D., DQMM/ORS/OGD
Through: Andrew Babiskin, Ph.D., Lead Chemist, DQMM/ORS/OGD
Lanyan (Lucy) Fang, Ph.D., Associate Director, DQMM/ORS/OGD

Reason for Consultation:

Amneal Pharmaceuticals, LLC (hereafter referred to as “Amneal” or “the applicant”) submitted an abbreviated new drug application (ANDA) 213950 for their product, generic Norelgestromin (NGMN) and Ethinyl Estradiol (EE) Transdermal System (TDS), 150 µg/day and 35 µg/day respectively¹. In support of their ANDA, Amneal has submitted a “pivotal, open label, balanced, randomized, two-treatment, two-sequence, two-period, single application, two-way crossover, bioequivalence (BE) with pharmacokinetic (PK) endpoints and adhesion Study of NGMN and EE Transdermal System, 150/35 µg per day manufactured by Amneal Pharmaceuticals LLC with XULANE® NGMN and EE Transdermal System 150 µg/35 µg per day manufactured for Mylan Pharmaceuticals Inc., in normal healthy, adult, human, female subjects under fasting conditions”. The reference and test products were applied on the abdomen of study participants. The 90% Confidence Intervals (CIs) for Area Under the concentration versus time Curves (AUC) and maximum concentrations (Cmax) for both EE and NGMN meet the BE criteria of 80.00-125.00%.²

The Reference listed drug (RLD) is Janssen Pharmaceuticals Inc.’s ORTHO EVRA® (NGMN and EE) TDS, 150/35 µg/day (NDA 021180; Approved on 11/20/2001), which has been discontinued, but not for safety or efficacy reasons

¹ Please note that we are using the strength as indicated in the product labeling (µg per day). The Orange Book refers to the product strength in terms of MG/24HR. Both units are used throughout this document.

² ANDA213950, Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D.
A213950N000DB-Review01-12182019.docx
(<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

per federal register determination. Per the Orange Book, the reference standard (RS) is Mylan's XULANE® (NGMN and EE) TDS (ANDA 200910, approved in April 16, 2014). In the pivotal BE study supporting ANDA 200910,³ the drug products XULANE® and ORTHO EVRA® TDSs were applied on the back of all study participants.

Residual drug analysis conducted by Mylan showed a higher delivery rate of EE (53.0 µg/day) for the RS than the current application (~22 µg/day) as summarized by Division of Bioequivalence (DB) III in the **Table 1** below.⁴ The results of the residual drug analysis for the RLD (ANDA 200910), RS (ANDA 200910, 213950 and 213977) and the generic products from ANDA 213950 and ANDA 213977 are summarized in the **Table 1** below.⁵ EE delivery for XULANE® is highlighted in yellow.

Table 1: Summary of residual drug analysis on EE extracted from ANDAs 200910, 213950 and 213977. Source: ANDA 213950, BE Review⁶. The application site for ANDAs 200910, 213950 and 213977 has been added to the original table obtained from ANDA 213950, BE Review.

	Mylan (A200910)		Amneal (A213950)		Teva (A213977)	
	RLD	XULANE®	XULANE®	Test	XULANE®	Test
Application site	Back		Abdomen		Abdomen	
EE Loading (µg)	750	530	530	289	518	534
residual (µg)			360 (11.9 % RSD)	138 (21.9 % RSD)	267 (33 %RSD)	316 (13% RSD)
(Range)	289	159	(b) (4)	(b) (4)	(b) (4)	(b) (4)
%residual	38.5	30.00	67.92	47.75	51.54	59.18

³ ANDA 200910, Division of Bioequivalence Review, Reviewer: Suman Dandamudi. Date: 06/05/2013.

⁴ V:\DIVISION\BIO\BIO3\Email Communications\ANDA 213950 Norelgestromin and Ethinyl Estradiol Transdermal System, presentations.

⁵ ANDA213950, Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D. A213950N000DB-Review01-12182019.docx

(<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

⁶ ANDA213950, Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D. A213950N000DB-Review01-12182019.docx

(<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

delivered (µg)	461 (26.9% RSD)	371 (24.3% RSD)	170	151	251	218
%delivery	61.5	70.00	32.08	52.25	48.46	40.82
delivery (µg/day)	65.9	53.0	24.3	21.6	35.9	31.1
Nominal Delivery (µg/day)	35 (RLD labeling)					

From the above table, based on residual analysis, large variability is observed around the % of EE delivered from the RS across several applications (ANDAs 200910, 213950 and 213977); delivery rates range from 24.3 to 53.00 µg/day. Based on the RLD labeling, EE is expected to be delivered at a 35 µg/day rate (nominal delivery rate). However, the actual delivery rate is higher than 35 µg/day in the ANDA 200910 BE study and lower than 35 µg/day in ANDA 213950.

Against this background, the Office of Pharmaceutical Quality (OPQ) was concerned that if an EE delivery rate of ~53 µg/day (RS, ANDA 200910) and (b) (4) µg/day (RLD, ANDA 200910) was assumed for the non-abdominal site, the total drug load needs to be 371~462 µg per TDS to be delivered over a 7-day period (i.e., 0% residual drug). However, in Amneal's Test product (ANDA 213950), the drug load is only 289 µg, and it may not be enough for 7 days of wearing period if the patch is applied at a non-abdominal site. Therefore, the OPQ team raised the question whether an additional BE study is warranted at a non-abdomen site to demonstrate BE of current Test product although from a quality perspective, the lower drug loading in Amneal's proposed product complies with the Residual Drug Guidance⁷ and is not an issue.⁸

During a meeting with the Division of Therapeutic Performance (DTP) in Office of Research and Standards (ORS) on 04/08/2020 to discuss OPQ's concern, DTP and DBIII discussed the following key points⁹:

1. It can be technically challenging to precisely and accurately estimate the amount of drug remaining in (or delivered by) a TDS during its duration of wear based upon a residual drug analysis.
2. The labeled strength (i.e., the nominal in vivo EE delivery rate) may not be accurate, itself, due to precision and accuracy issues with the methodology by which it was calculated and due to some historical challenges with the underlying data that were used to calculate this nominal rate.

⁷ FDA Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems (August 2011). Accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/residual-drug-transdermal-and-related-drug-delivery-systems>

⁸ V:\DIVISION\BIO\BIO3\Email Communications\ANDA 213950 Norelgestromin and Ethinyl Estradiol Transdermal System, Residual Drug - Ortho Evra ANDAs OPQ 03172020.pptx

⁹ ANDA213950, A213950N000DB-MeetingMinutes01-04082020.docx (<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

3. Based upon recommendations in FDA's Residual Drug Guidance¹⁰, an ANDA applicant is encouraged to develop "a product to deliver the optimum amount of drug across the skin while minimizing the amount of drug load, thus resulting in the least possible amount of residual drug substance." However, the applicant is expected not to reduce the drug loading to such an extreme that there is no longer a sufficient excess of drug available within the TDS to maintain the concentration gradient and driving force to ensure that the prospective generic TDS sustains the same rate and extent of drug delivery as the reference TDS at each point in time, throughout the wear period.
4. Comparable drug delivery between the Test and Reference drug products throughout the wear period depends not only on loading drug amount and residual drug left in the TDS but also on the TDS design and formulation (including the inactive ingredients).
5. ORS pointed out that there appears to be perceptibly lower mean plasma concentrations in Amneal's Test product (compared to the RS) after 72 hours and until 168 hours, based on the mean concentration vs time profiles from the BE study supporting ANDA 213950. This raised a potential concern about whether the lower mean plasma concentrations observed with the Test product after 3-days of wear may be due to an excessively depleted drug load that might have left an insufficient excess of drug available within the TDS after 72 hours to maintain the concentration gradient and driving force to sustain the same rate and extent of drug delivery as the reference TDS after 72 hours, which may ultimately indicate a sub-optimal initial loading dose of EE and/or a sub-optimal TDS design and/or formulation.
6. Per NDA 021180 Clinical Pharmacology review, the targeted steady state concentration (C_{ss}) of EE is 25-75 pg/mL, a 3-fold range for optimum efficacy and it is noted that the decrease in plasma concentration of EE is ~33% (from (b) (4) pg/mL) for the test product in the current application.

The purpose of this review is to answer a consult request from the DBIII to the Division of Quantitative Methods and Modeling (DQMM) related to ANDA 213950 regarding employing modeling and simulation methodologies to address concerns on potential insufficient EE loading dose for the ANDA 213950 Test product.

DBIII is seeking expert opinion from DQMM on the following questions (*in italics*):

1. *Please estimate the amount of EE delivered by the test and reference TDS on a non-abdominal site (i.e., back) based upon a deconvolution of the pharmacokinetic (PK) data.*

¹⁰ FDA Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems (August 2011). Accessible at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/residual-drug-transdermal-and-related-drug-delivery-systems>

2. *Please use a physiologically based model to predict the PK of EE across the back (as a non-abdominal site) based on diffusion parameters obtained for the test product from the abdominal application of TDS.*

Executive Summary:

To obtain an insight on the amount of EE that is being released in vivo from the RLD (ORTHO EVRA®), RS (XULANE®) and Test (Amneal) products when applied on patients and decipher the role of the application site (abdomen vs back) to the systemic exposure and PK profiles observed following application of these products in the clinical setting^{11,12}, dermal PBPK models were developed for the RLD, RS and the Test (Amneal) product using the Multi-Phase Multi-Layer (MPML) MechDermA module within Simcyp Simulator v19. Clinical PK data following RLD and RS patch application on the back and the abdomen, respectively, as well as drug product information from NDA 021180 and ANDA 200910 were leveraged for model validation.

Deconvolution of the observed mean PK profile for EE (ANDA 213950, study ESTN/2018/1607) following application of the Test product in the abdomen showed that 38% of the loaded EE dose is delivered by the end of the wear period (109.8 µg). Following the same methodology, deconvolution of the observed mean PK profile for EE following application of the RS on the abdomen showed that 22% of the loaded EE dose is delivered by the end of the wear period (117 µg). Predicted delivery rates were comparable between the Test and the RS throughout the wear period.

The validated dermal PBPK models for the Test and RS products were leveraged towards predicting systemic exposure following patch application on the back of virtual healthy volunteers assuming the same in vivo drug release profile on the back as on the abdomen. The absence of notable differences on the predicted mean PK profiles between the Test and the RS following application on the back suggest that the Test product and the RS are expected to be BE following patch application on the back. It was predicted that, similarly to the case of the abdomen, 38% of the loaded EE dose will be delivered by the end of the wear period (109.8 µg) from the Test product when applied on the back. Therefore, no EE depletion is expected when the Test product is applied on the back under labeled conditions.

In our modeling and simulation work, we assumed that patches release drug at the same rate regardless of the application site, which is consistent with the current knowledge of TDS function. As such, any differences in PK exposure

¹¹ Fertil Steril. 2002 Feb;77(2 Suppl 2): S3-12. Pharmacokinetic Overview of Ortho Evra/Evra. Larry S Abrams, Donna Skee, Jaya Natarajan, Frankie A Wong.

¹² Br J Clin Pharmacol 2002 Feb;53(2):141-6. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinylloestradiol at Four Application Sites. Larry S Abrams, Donna M Skee, Jaya Natarajan, Frankie A Wong, Gary D Anderson.

following application at different application sites would be the result of differences in skin physiology between application sites.

As for the variability in EE plasma concentrations following the application of the RS product observed across ANDA 200910, ANDA 213950 and ANDA 213977, a number of other confounding factors that can drive this besides application site – number of subjects, study-to-study differences in skin physiology and drug distribution and elimination, and study conduct (e.g., how patch was applied and conditions at which patch was applied). In our analysis of all available PK data related to EE from these patches from the RLD and RS, we mostly observe consistency in EE PK profiles between different studies and application sites, but with one anomaly – the PK BE study with the back as the application site used for the approval of the RS XULANE® (ANDA 200910) – where both RLD and RS demonstrate significantly higher concentrations than other PK studies conducted with these products and also with the back as the application site. It is important to note that an overlay was utilized to support the RLD and RS TDS in the in vivo BE study with PK endpoints supporting ANDA 200910 which may have contributed to the higher EE exposure observed for both the RLD and RS products in this study compared to EE exposure observed for these products in other in vivo BE studies with PK endpoints (NDA 021180, ANDA 213950, ANDA 213977).

In all, our simulations suggest that BE would be demonstrated between Test and RS in a BE study with the back as the application site, if no overlay is used. Additionally, there would be sufficient amount of EE in the Test patch to cover the period of application since deconvolution of the mean PK profiles indicated that 38% of the loaded EE amount is released from the Test product by the end of the wear period on the back. However, if an overlay is used (similar study design as ANDA 200910) when the Test product was applied on the back, simulations indicated that 77% of the loaded EE amount (0.289 mg) will be delivered by the end of the wear period.

In conclusion, our analysis indicates that the Test and RS are expected to be BE and no EE depletion is expected for the Test drug product when the product is applied on the back of healthy volunteers under the labeled use conditions (no overlay).

Response:

- 1. Please estimate the amount of EE delivered by the test and reference TDS on a non-abdominal site (i.e., back) based upon a deconvolution of the pharmacokinetic (PK) data.*

Dermal physiologically-based pharmacokinetic (PBPK) modeling was employed to describe the absorption through the skin and the systemic disposition of EE following the application of XULANE® (NGMN and EE) TDS (RS, ANDA 200910) and the generic NGMN and EE TDS, 150/35 µg/day developed by Amneal (ANDA 213950). After validating model performance in predicting systemic exposure

following application of the ORTHO EVRA® (RLD) and RS TDSs on the back and abdomen, clinical PK data were leveraged from the approved ANDA 200910 and the currently under review ANDA 213950 and ANDA 213977 to predict an in vivo drug release profile from the RS and the Test product.

The dermal PBPK model developed for the RS product (ANDA 213950) predicted that by the end of the wear period 0.117 mg (22% of the loaded amount) of EE will be delivered and 78% of the initially loaded EE amount remains in patch at the time of removal from the back. In the case of the Test product (ANDA 213950), the product-specific dermal PBPK model for the Test product predicted that by the end of the wear period 0.1098 mg (38% of the loaded amount) of EE will be delivered and 62% of the initially loaded EE amount will remain in the patch at the time of removal from the abdomen.

2. Please use a physiologically based model to predict the PK of EE across the back (as a non-abdominal site) based on diffusion parameters obtained for the test product from the abdominal application of TDS.

A dermal PBPK model was developed for the Test product (ANDA 213950) to describe the absorption through the skin and the systemic disposition of EE following the application of the product on the abdomen of healthy female subjects. To that end, the clinical PK data supporting ANDA 213950 (pivotal BE study ESTN/2018/1607) were used to predict the in vivo EE release from the Test product following application on the abdomen of study participants (Figure 1A) which is in turn was utilized towards simulating the systemic PK profile for EE after product application on the back of virtual healthy volunteers (Figure 1B).

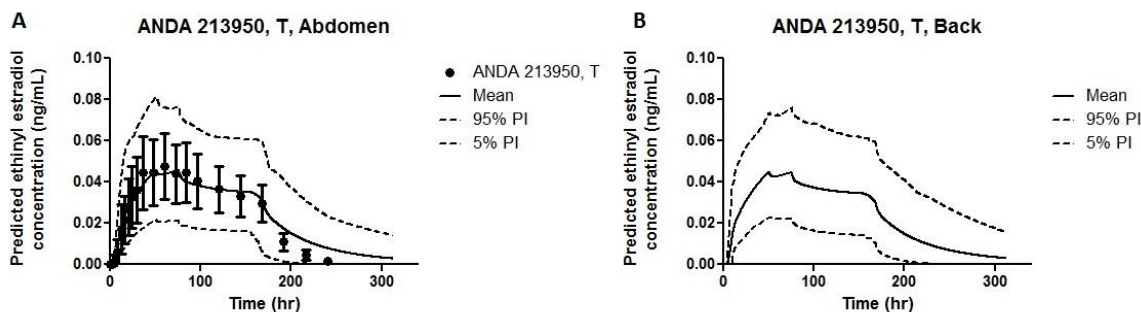


Figure 1: Observed (solid black) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test product (ANDA 213950) on the abdomen of healthy volunteers¹³ (A) and on the back of virtual healthy volunteers (B). Simulated scenarios were the same as the study design of the pivotal BE study supporting ANDA 213950.

¹³ ANDA213950, Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D. A213950N000DB-Review01-12182019.docx

Model predictions suggested that the predicted mean PK profile in the back (C_{max} 44.9 pg/mL, AUC 7240 pg*hr/mL) is similar to the predicted mean PK profile in the abdomen (C_{max} 45.8 pg/mL, AUC 7538 pg*hr/mL) and similar to the observed mean PK profile following application on the abdomen (C_{max} 49.6 pg/mL, AUC 6724 pg*hr/mL, ANDA 213950, study ESTN/2018/1607). Deconvolution of the observed mean PK profile for EE following application of the Test product on the abdomen showed that 38% of the loaded EE dose was delivered by the end of the wear period. The same analysis revealed that initial delivery rate (0 to 50 hours) was similar to the one reported by the applicant on their residual drug analysis (22.2 µg/day was the model predicted delivery rate while 21.6 µg/day was the one estimated by the applicant). However, the developed model predicted a gradual decrease in this delivery rate from t=50 hour until the end of the wear period while the residual drug analysis provided by the applicant assumes constant release rate throughout the wear period. The overlaid mean (95% and 5% prediction intervals) predicted PK profiles following application of the Test product in the abdomen and the back are shown in **Figure 2** below.

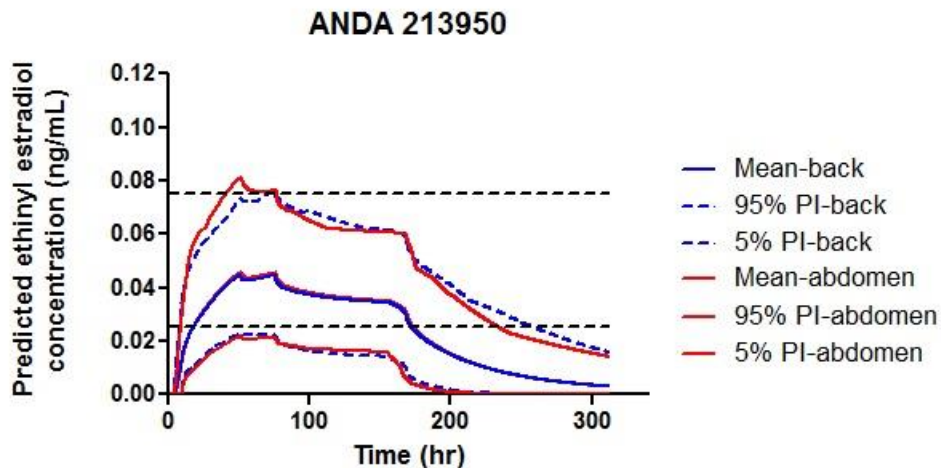


Figure 2: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test product (ANDA 213950) on the abdomen of healthy volunteers (red) and on the back of virtual healthy volunteers (blue). Simulated scenarios were the same as the study design of the pivotal BE study supporting ANDA 213950. Dashed lines represent the targeted steady state concentration (C_{ss}) of EE 25-75 pg/mL per the NDA 021180 Clinical Pharmacology review.

Background:

Indication, Drug Substance, and Mechanism of Action

The drug products ORTHO EVRA®, XULANE® and the Test Amneal NGMN and EE TDS, 150 /35 µg/day under ANDA 213950 are combination products that contain NGMN and EE at certain amounts. The ORTHO EVRA® TDS has a 20 cm² contact area and contains 6.00 mg NGMN and 0.75 mg EE. The XULANE® TDS has a contact surface area of 14 cm². It contains 4.86 mg NGMN, USP and 0.53 mg EE, USP. Finally, the Test product (ANDA 213950) has a contact area of 12.5 cm² and it contains 3.15 mg NGMN, USP and 0.289 mg EE, USP.

The chemical structures of NGMN and EE are provided below:

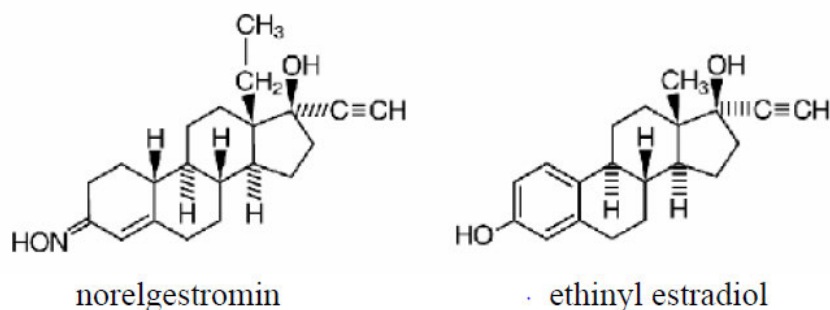


Figure 3: Chemical structure of NGMN and EE.

ORTHO EVRA®¹⁴ is an estrogen/progestin combination hormonal contraceptive (CHC), indicated for the prevention of pregnancy in women who elect to use a transdermal patch.

NGMN is the active progestin largely responsible for the progestational activity that occurs in women following application of ORTHO EVRA®. NGMN is also the primary active metabolite produced following oral administration of norgestimate (NGM), the progestin component of the oral contraceptive products ORTHO-CYCLEN® and ORTHO TRI-CYCLEN®.

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

ORTHO EVRA® uses a 28-day (four-week) cycle. Apply a new patch to the upper outer arm, abdomen, buttock or back each week for three weeks (21 total days). Week Four is patch-free.

¹⁴ ORTHO EVRA®, (norelgestromin/ethinyl estradiol transdermal system), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s0481bl.pdf

Patients prescribed ORTHO EVRA®¹⁵ are warned of potential serious adverse events. Based on the drug label, they are strongly advised not to smoke when using hormonal contraceptives such as the products in hand due to an increased risk for serious cardiovascular adverse events.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING, RISK OF VENOUS THROMBOEMBOLISM, and PHARMACOKINETIC PROFILE OF ETHINYL ESTRADIOL

Cigarette Smoking and Serious Cardiovascular Risks

Cigarette smoking increases the risk of serious cardiovascular events from hormonal contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, hormonal contraceptives, including ORTHO EVRA, should not be used by women who are over 35 years of age and smoke.

Risk of Venous Thromboembolism

The risk of venous thromboembolism (VTE) among women aged 15-44 who used the ORTHO EVRA patch compared to women who used several different oral contraceptives was assessed in five U.S. epidemiologic studies using electronic healthcare claims data. The relative risk estimates ranged from 1.2 to 2.2; one of the studies found a statistically significant increased relative risk of VTE for current users of ORTHO EVRA [see *Warnings and Precautions (5.1)*].

Pharmacokinetic (PK) Profile of Ethinyl Estradiol (EE)

The PK profile for the ORTHO EVRA patch is different from the PK profile for oral contraceptives in that it has a higher steady state concentrations and a lower peak concentration. Area under the time-concentration curve (AUC) and average concentration at steady state (C_{ss}) for EE are approximately 60% higher in women using ORTHO EVRA compared with women using an oral contraceptive containing 35 mcg of EE. In contrast, the peak concentration (C_{max}) for EE is approximately 25% lower in women using ORTHO EVRA. It is not known whether there are changes in the risk of serious adverse events based on the differences in PK profiles of EE in women using ORTHO EVRA compared with women using oral contraceptives containing 30-35 mcg of EE. Increased estrogen exposure may increase the risk of adverse events, including VTE [see *Warnings and Precautions (5.2)* and *Clinical Pharmacology (12.3)*].

Drug product

This consult is relevant to three NGMN and EE, 150/35 µg/day, TDSs: (a) ORTHO EVRA® (NDA 021180), (b) XULANE® (NDA 200910) and (c) ANDA 213950 Test product.

ORTHO EVRA® (EE; NGMN) extended release film 150/35 µg/day; TDS (NDA 021180)¹⁶:

ORTHO EVRA® is a transdermal patch with a contact surface area of 20 cm² containing 6 mg NGMN and 0.75 mg EE.

ORTHO EVRA® is a thin, matrix-type transdermal contraceptive patch consisting of three layers. The backing layer is composed of a beige flexible film consisting of a low-density pigmented polyethylene outer layer and a polyester inner layer. It

¹⁵ ORTHO EVRA®, (norelgestromin/ethinyl estradiol transdermal system), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s0481bl.pdf

¹⁶ ORTHO EVRA®, (norelgestromin/ethinyl estradiol transdermal system), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s0481bl.pdf

provides structural support and protects the middle adhesive layer from the environment. The middle layer contains polyisobutylene/polybutene adhesive, crospovidone, non-woven polyester fabric and lauryl lactate as inactive components. The active components in this layer are the hormones, NGMN and EE. The third layer is the release liner, which protects the adhesive layer during storage and is removed just prior to application. It is a transparent polyethylene terephthalate (PET) film with a polydimethylsiloxane coating on the side that is in contact with the middle adhesive layer.

The composition of the product is provided below (Table 2).

Table 2: Formulation composition of ORTHO EVRA® (EE; NGMN) extended release film 150/35 µg/day; transdermal delivery system (NDA 021180), 6 mg/0.75 mg per 20 cm² patch; 2.00%/0.25% of the dried adhesive.¹⁷

Components	Nominal Amount (mg/patch)	% w/w
Norelgestromin	6.00	2.00
Ethinyl estradiol, USP, Ph. Eur	0.75	0.25
Polyisobutylene/polybutene adhesive blend	(b) (4)	
Lauryl lactate		
Crospovidone, Micronized, NF, Ph. Eur		
(b) (4)		
Polyester nonwoven backing support for drug in adhesive		
(b) (4)		

XULANE® (EE; NGMN) extended release film 150/35 µg/day; TDS (NDA 200910)¹⁸:

XULANE® is a TDS with a contact surface area of 14 cm². It contains 4.86 mg NGMN, USP and 0.53 mg EE, USP, and its delivery rate is approximately 150 µg of NGMN and 35 µg of EE per day. The composition of the product is provided below (Table 3).

¹⁷NDA 021180, Chemistry and Manufacturing Controls Review #1, Date 10-12-01, Reviewer: Amit K. Mitra, Ph.D.

¹⁸ ANDA 200910, Chemistry and Manufacturing Controls Review #5, Date 11/08/13, Reviewer: Guohua Li, Ph.D.

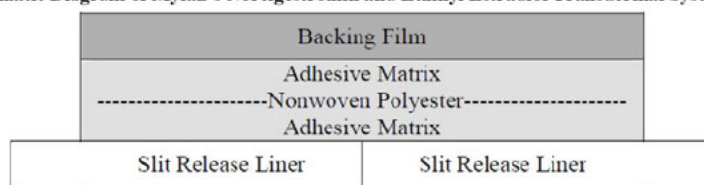
Table 3: Formulation composition of XULANE® (EE; NGMN) extended release film 150/35 µg/day; transdermal delivery system (ANDA 200910).¹⁹

Table 2.1 Product Comparison - Norelgestromin and Ethinyl Estradiol Transdermal System and Ortho Evra®

Component	Function	% w/w	
		Mylan Norelgestromin and Ethinyl Estradiol Transdermal System	Ortho Evra® (Estimated)
Norelgestromin	Active Ingredient	2.31	2.00
Ethinyl Estradiol	Active Ingredient	0.25	0.25
Polyisobutylene Adhesive	(b) (4)	(b) (4)	(b) (4)
Oleyl Alcohol			
Lauryl Lactate			
Dipropylene Glycol			
(b) (4) Mineral Oil			
Polybutene			
Crospovidone			
(b) (4)			(b) (4)
			(b) (4)

XULANE® TDS contains two active pharmaceutical ingredients (API) that are both dissolved in a pressure-sensitive adhesive matrix. Mylan’s NGMN and EE TDS is BE to the ORTHO EVRA® TDS. It contains three layers. The outermost backing film layer is a pigmented polyethylene / polyester film. The middle layer is the polyisobutene adhesive matrix containing the two APIs. It also contains several inactive ingredients, namely oleyl alcohol, dipropylene glycol, crospovidone, nonwoven polyester, and light mineral oil. The third layer is a release liner that is slit near the middle to facilitate removal prior to use. This liner is a transparent, fluoropolymer coated polyester film and both pieces are removed from the patch and discarded prior to use.

Schematic Diagram of Mylan’s Norelgestromin and Ethinyl Estradiol Transdermal System



Note: Diagram is not to scale

In vitro permeation testing²⁰ comparing XULANE® to ORTHO EVRA® TDS has been conducted by Mylan towards optimizing their formulation. This study was performed using the same test articles that were used for the pivotal PK BE study, ORTH-0942: Mylan NEETS Lot R6A0014 and Ortho Evra® Lot 7LM5212 (it should be noted that the study conditions could not be located by the current reviewer). The

¹⁹ ANDA 200910, Chemistry and Manufacturing Controls Review #5, Date 11/08/13, Reviewer: Guohua Li, Ph.D.

²⁰ ANDA 200910, Chemistry and Manufacturing Controls Review #5, Date 11/08/13, Reviewer: Guohua Li, Ph.D.

study outcomes are provided below. The two products appear to have comparable skin permeation profiles (Figure 4).

Figure A-1.1a: In Vitro Skin Permeation Rate of Ethinyl Estradiol from Pivotal Pharmacokinetic Bioequivalence Study Lots

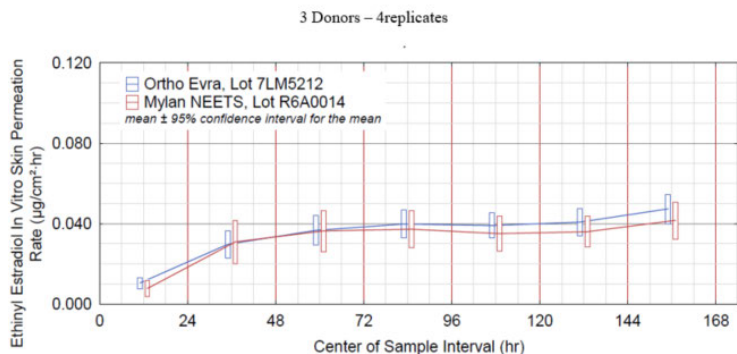


Figure A-1.1b: In Vitro Skin Permeation Rate of Norelgestromin from Pivotal Pharmacokinetic Bioequivalence Study Lots

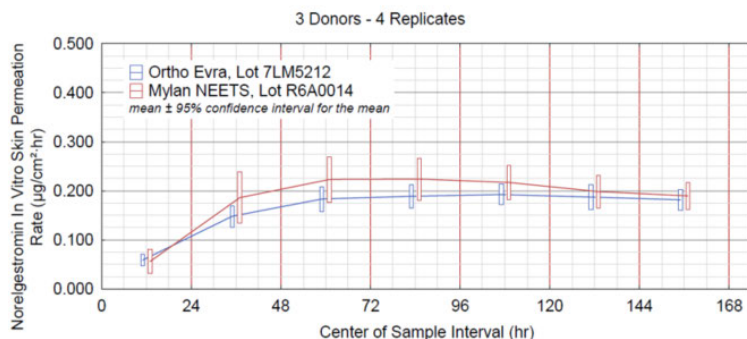


Figure 4: Profile of in vitro skin permeation rate of EE (top graph) and NGMN (bottom graph) for XULANE® to ORTHO EVRA® TDSs²¹.

Generic NGMN and EE TDS, 150/35 µg/day (ANDA 213950):

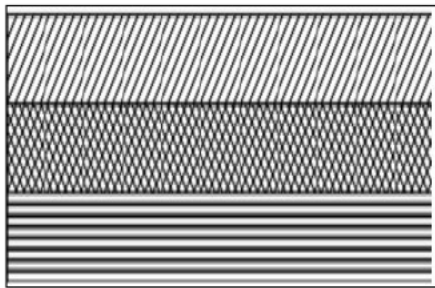
Generic NGMN and EE TDS, 150/35 µg/day (ANDA 213950) is a matrix-type TDS with a contact surface area of 12.5 cm². It contains 3.15 mg NGMN, USP and 0.289 mg EE, USP. The composition of the product is provided below (Table 4).

²¹ ANDA 200910, Chemistry and Manufacturing Controls Review #5, Date 11/08/13, Reviewer: Guohua Li, Ph.D.

Table 4: Formulation composition of generic NGMN and EE TDS, 150/35 µg/day (ANDA 213950).²²

Ingredients	Quantity in mg/patch	Quantity in %w/w	Function
Ethinyl Estradiol, USP (Micronized)	0.289	0.22	API
Norelgestromin, USP	3.15	2.4	API
Polyisobutylene/Polybutene Adhesive (b) (4)	(b) (4)	(b) (4)	(b) (4)
Polybutene (b) (4)			
Crospovidone, NF (b) (4)			
Oleyl Alcohol, NF (b) (4)			
Dipropylene Glycol			
*Ethyl Acetate, NF (b) (4)			
(b) (4)			
Total Weight of Adhesive Ingredients	(b) (4)	100	-
(b) (4)			

Similarly, to the XULANE® TDS, the generic NGMN and EE TDS, 150/35 µg/day (ANDA 213950) contains three layers. The outermost backing film layer is a pigmented polyethylene/polyester film. The middle layer is the adhesive layer containing the active ingredients and penetration enhancers (oleyl alcohol, dipropylene glycol) and the rest of the inactive ingredients pre the formulation composition Table 4 above. The third layer is a protective liner with silicone coating that is removed prior to use.



- | |
|--|
| 1) Backing Film: Pigmented Polyethylene and Polyesterfilm |
| 2) Adhesive Layer: Norelgestromin, USP, Ethinyl Estradiol USP (micronized), DuroTak (b) (4) PIB/Polybutene Adhesive, Polybutene (b) (4), Dipropylene Glycol, Crospovidone (b) (4) and Oleyl Alcohol |
| 3) Protective liner: Polyethylene terephthalate film with silicone coating |

²² ANDA213950, Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D. A213950N000DB-Review01-12182019.docx (<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>)

To support the drug product development program^{23, 24}, in vitro permeation studies were performed with the objective of optimizing formulation components such as the amounts of penetration enhancers. Briefly, human cadaver skin (HCS, back) and a Hanson Franz diffusion cell (1.766 cm² available diffusion area) were used. Over-sized patches were cut to cover the diffusional area of the diffusion cell. The receptor solution (7 mL) was 0.9% NaCl with 2-Hydroxyl propyl β- cyclodextrin and was sampled at selected time points for drug content. The studies were performed at 32 ± 0.5°C and ambient humidity. The drug content results were used to quantify the drug flux over the course of the experiment.

Optimized products that appeared to be similar to the RS in the in vitro permeation study conditions described above were evaluated in two failed pilot BE studies. The test product was reformulated: an (b) (4) (b) (4) were performed as a result of the first pilot study. (b) (4)

(b) (4) were performed following a second failed pilot BE study. That final optimized patch was used for the pivotal BE study that is the first passing BE study for this product (Batch No. PW-ST-18020A).

Skin flux studies were run using the PW-ST-18020A (average of three skin donors) batch against XULANE® and were found to closely match the RS as shown in the Figure 5. PW-ST-18020A was the batch used for the pivotal BE study for ANDA 213950. Additional in vitro permeation testing was conducted to assess the performance of the Test compared to the RS under different temperature conditions (32 and 42°C).

²³ ANDA 213950, 32p2-pharmaceutical-dev-report.pdf, EDR, accessed 06/23/2020.

²⁴ ANDA 213950, 32p2-annexure-2-invitro-permeation-report, EDR, accessed 06/23/2020.

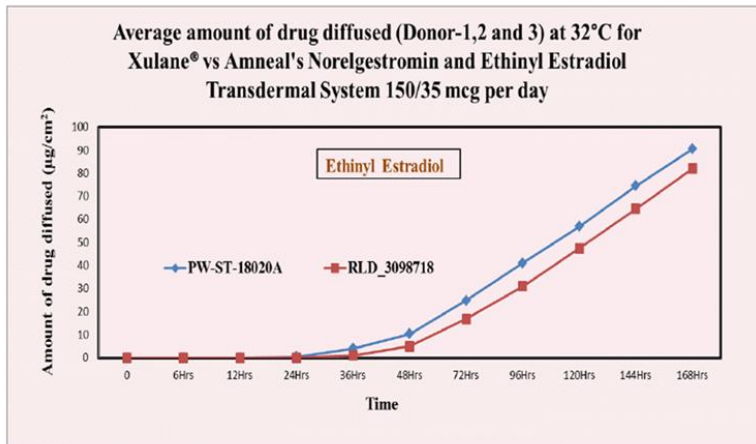


Figure 2 Average amount of Ethinyl Estradiol diffused (Donor-1, 2 and 3) at 32°C

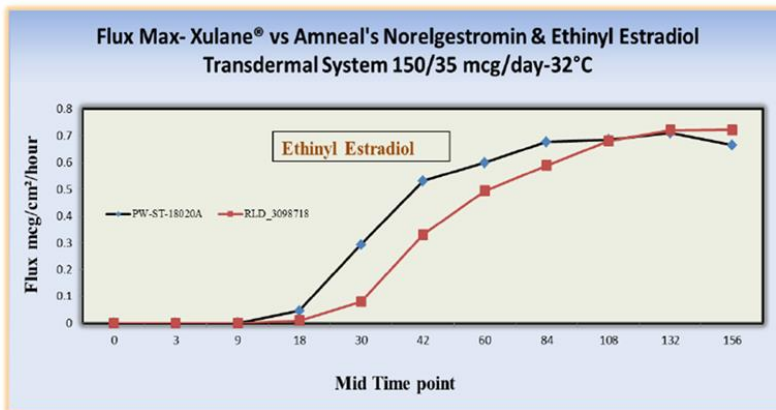


Figure 3 Ethinyl Estradiol Flux rate at 32°C

Figure 5: Average amount (top) and flux rate (bottom) for EE calculated from in vitro skin permeation studies for the Test and the RS product in support of ANDA 213950.²⁵

To support ANDA 213950, the applicant conducted the pivotal in vivo BE study ESTN/2018/1607 to demonstrate BE between their generic TDS and the RS XULANE®. **Table 5 and Figure 6** below summarize the study design and study outcomes; the TDS was applied on the abdomen of the study participants. Per the pending review by DB III²⁶, the two products were found to be BE.

²⁵ ANDA 213950, 32p2-annexure-2-invitro-permeation-report, EDR, accessed 06/23/2020.

²⁶ ANDA 213950, Division of Bioequivalence Review, Reviewer: Madhusudana Rao Chaluvadi, Ph.D., R.Ph., BCPS. Date: 6/5/2013.

Table 5: Summary of pivotal in vivo BE study ESTN/2018/1607 supporting ANDA 213950.

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)***						Study Report Location
					C _{max} (pg/mL)	*T _{max} (h)	AUC _(0-t) (pg.h/mL)	AUC _(0-∞) (pg.h/mL)	t _{1/2} (h)	K _a (1/h)	
Ethinyl Estradiol											
ESTN/2018/1607	A Pivotal, Open Label, Balanced, Randomised, Two-Treatment, Two-Sequence, Two-Period, Single Application, Two-Way Crossover, Bioequivalence with Pharmacokinetic Endpoints and Adhesion Study of Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day manufactured by Amneal Pharmaceuticals LLC with Xulane (Norelgestromin and Ethinyl Estradiol Transdermal System 150 mcg/35 mcg per day manufactured for Mylan Pharmaceuticals Inc., Morgantown, WV 26505 U.S.A in Normal Healthy, Adult, Human, Female Subjects under Fasting Conditions.	A randomised, open label, balanced, two treatment, two period, two sequence, single application, crossover design.	Test Product - T Norelgestromin and Ethinyl Estradiol Transdermal System 150/35 mcg per day Patch 150/35 mcg per day Patch Transdermal [Batch # PW-ST-18020A]	79** completing (#F) Healthy subjects 30.29 Years (22-34)	49.6 ± 16.7 (33.6%)	60.00 (36.00 - 144.00)	6724 ± 2140 (31.8%)	6789 ± 2150 (31.7%)	18.6 ± 3.59 (19.3%)	0.0386 ± 0.0074 (19.2%)	Module 5.3.1.2
			Reference Product-R: Xulane® (norelgestromin and Ethinyl estradiol transdermal system) 150/35 mcg per day Patch 150/35 mcg per day Patch Transdermal		50.1 ± 18.4 (36.7%)	84.00 (36.00 - 168.05)	7334 ± 2796 (38.1%)	7434 ± 2840 (38.2%)	18.3 ± 3.73 (20.4%)	0.0393 ± 0.0076 (19.4%)	

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Ethinyl Estradiol)

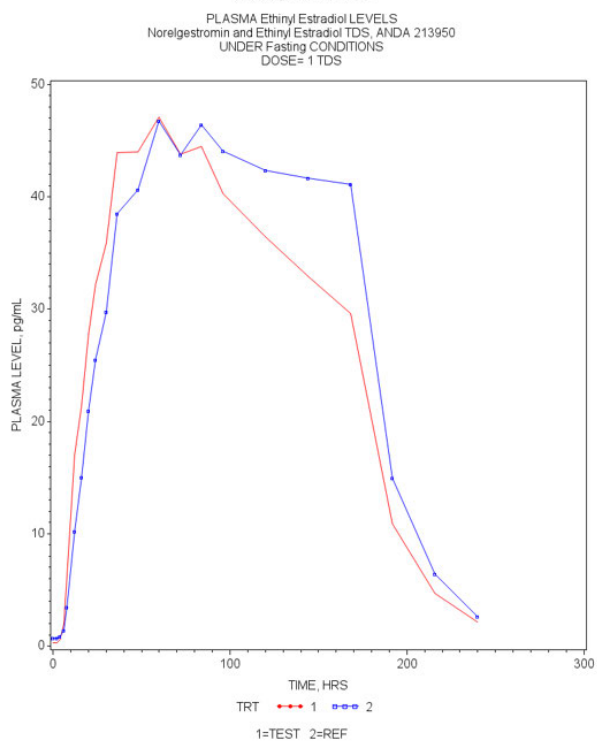


Figure 6: Mean EE PK profiles for Test (Amneal Test product) and RS products from the pivotal in vivo BE study ESTN/2018/1607 supporting ANDA 213950.

Regulatory History related to this consult

ORTHO EVRA® (NGMN and EE) TDS, 150/35 µg/day (NDA 021180; Approved on 11/20/2001) is the RLD (application holder: Janssen Pharmaceuticals Inc.) It is currently discontinued not for safety or efficacy reasons per federal register determination. Per the Orange Book, the XULANE® (NGMN and EE) TDS (ANDA 200910, approved in April 16, 2014, application holder: Mylan Pharmaceuticals) is the current RS (Table 6).

Table 6: Approved TDSs containing a combination of active ingredients: NGMN and EE. Orange Book accessed on 06/23/2020.

Mkt .Status	Active Ingredient	Proprietary Name	Appl. No.	Dosage Form	Route	Strength	RLD	RS	Applicant Holder	Approval Date
RX	ETHINYL ESTRADIOL; NORELGESTRO MIN	XULANE	A200910	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24 HR; 0.15MG/24 HR		S	MYLAN TECHNOLOG IES INC	16 April, 2014
DISCN	ETHINYL ESTRADIOL; NORELGESTRO MIN	ORTHO EVRA	N02180	FILM, EXTENDED RELEASE	TRANSDERMAL	0.035MG/24 HR; 0.15MG/24 HR ^s	R L D		JANSSEN PHARMACEU TICALS INC	20 Novem ber, 2001

§ **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**²⁷

Currently, there are no other approved generic products (outside of the RS) referencing either the RLD or RS. There are two pending ANDAs: 213950 and ANDA 213977. There were two ANDAs that were reviewed previously for this product (ANDA 078882 and 079037); However, both the applications were subsequently withdrawn.

Labeling for the ORTHO EVRA® patch²⁸:

The potency of ORTHO EVRA® is expressed as “rate of drug release” in the Orange Book, unlike other transdermal drug products. Since generic drug products generally have different drug release mechanism, they may contain different amounts of drug content and still can be BE to the respective reference products in the rate and extent of absorption. For example, XULANE® (NGMN and EE) TDS (ANDA 200910) contains 4.86 mg of NGMN and 0.53 mg of EE per patch and these amounts are different when compared with ORTHO EVRA® patch, a product it has shown to be BE to.

Based on the review of the controlled correspondence 07-0512²⁹, the following are the general considerations for TDSs: “*Transdermal products are considered*

²⁷

https://darrrts.fda.gov/darrrts/faces/ViewDocument?documentId=090140af8016a07b&_afRedirect=1609615673544456

²⁸ ANDA200910, Addendum to Division of BE Review, Reviewer: Suman Dandamudi, Ph.D., date: 02/04/2014.

²⁹ A:\OGDS6\Controls\2007-docs, 07-0512.pdf

as extended release drug products. The strength of a transdermal product is related to the amount of active ingredient that is delivered into the blood stream over a defined period of time, and not to amount of active ingredient initially in the patch. The amount of active ingredient in the generic product may differ from the amount of active ingredient in the RLD as long as the amount of the active ingredient absorbed into the blood stream in both products is equivalent. The difference in the amount of the active ingredient in the proposed generic compared to the RLD would have to be justified, regardless of equivalent pharmacokinetic and bioequivalence data”.

The ORTHO EVRA® patch was approved under NDA 021180 on November 20, 2001 as a TDS delivering 150/20 (NGMN/EE) µg/day. In 2006, the reference drug product labeling has been revised to omit the (b) (4)³⁰. The current RLD labeling states the following under Description section: “ORTHO EVRA is a combination transdermal contraceptive system with a contact surface area of 20 cm². It contains 6 mg NGMN and 0.75 mg EE”.

For a detailed description of the NDA 021180 sponsor rationale and the regulatory history relevant to this label change, refer to the Appendix.

Product-Specific Guidance

In May 2009, the Agency published the current PSG for EE; MG MN extended release film 150/35 µg/day³¹ referencing ORTHO EVRA® and XULANE®. The Agency recommends three studies in the current PSG:

Study 1:

Type of study: BE study with PK endpoints
Design: Single dose, two-treatment, two-period crossover in vivo study
Strength: 0.035 mg/24 hr; 0.15 mg/24 hr
Subjects: Healthy non pregnant, non-lactating females, who are candidates for hormonal contraception

Study 2:

Type of study: Adhesion study
Design: Single dose, two-treatment, two-period crossover in vivo study
Strength: 0.035 mg/24 hr; 0.15 mg/24 hr
Subjects: Healthy non pregnant, non-lactating females, who are candidates for hormonal contraception

Study 3:

Type of study: Skin irritation and sensitization study

³⁰ DARRTS for NDA 021180: WILLIAMSON, ZETA-MAE C 05/17/2006 N/A 05/17/2006 REV-RPM-05(General Review) Supplement-20 (Labeling) Archive

³¹ Ethinyl Estradiol; Norelgestromin extended release film 150 µg /35 µg/day; transdermal delivery system, NDA 021180 and ANDA 200910, recommended March 2009 and revised in July 2009 and October 2016 and October 2018,
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021180.pdf

Design: Randomized, evaluator-blinded, within-subject repeat design, in vivo
Strength: 0.035 mg/24 hr; 0.15 mg/24 hr (Dose: one-half of the 0.035 mg/24 hr; 0.15 mg/24 hr TDS)
Subjects: Healthy non pregnant, non-lactating females, who are candidates for hormonal contraception

The development of the Agency’s recommendations originally published in March 2009 were reflected in controlled correspondence 07-512³². Since May 2009, the PSG has been revised in July 2009, October 2016 and October 2018³³.

Controlled correspondence:

The controlled correspondences (CC) referencing NDA 021180/ANDA 200910 submitted to the Agency by Amneal are listed in the **Table 7** below.

Table 7: Controlled correspondence (CC) submitted by Amneal Pharmaceuticals referencing NDA 021180/ANDA 200910.

CC#/Date	Question	Status/Response
15728669 ³⁴ , July 16, 2017	IIG evaluation on certain inactive ingredients per the applicant’s proposed maximum daily intake (MDI).	Closed/ proposed inactive ingredients amounts were found acceptable.
16990170 ³⁵ , August 14, 2017	IIG evaluation on the same inactive ingredients as CC#15728669 for lower MDI amounts.	Closed/ proposed inactive ingredients amounts were found acceptable.
10376677 ³⁶ , September 26, 2016	Concurrence in using XULANE® as the reference standard (RS) for their generic drug development when conducting in vivo bioequivalence studies.	Closed/ the Agency updated their guidance to indicate XULANE® as the reference standard since the RLD ORTHO EVRA® was discontinued.

³² A:\OGDS6\Controls\2007-docs, 07-0512.pdf

³³ <https://panorama.fda.gov/project/view?ID=59cb018100222ab85f25663db5489f02> ,
<https://panorama.fda.gov/project/view?ID=5d35bdd9003eee01288f6aab508f5e81> ,
<https://panorama.fda.gov/project/view?ID=5783f4ec0016ebe0a3e48ee4f4b384e1>

³⁴ <https://panorama.fda.gov/task/view?ID=5947d1d900b562ae14cf6f8131bf06b4>

³⁵ <https://panorama.fda.gov/task/view?ID=599455be00605c7b4f24b17aff2ad069>

³⁶ <https://panorama.fda.gov/project/view?ID=57e9786d0010871c40723e1a4499de78>

27999717 ³⁷ , December 17, 2018	Clarification on the inclusion criterion for all in vivo studies included in current PSG according to which: “subjects with an intact uterus who have a baseline vaginal ultrasonography demonstrating inactive endometrial lining with endometrial thickness less than 4 mm” may participate in the Agency-recommended studies.	Closed/ The Agency agreed that not all subjects would be comfortable with the approach, and that the criterion would lead to unpredictable enrollment and communicated that the Agency concurs that this inclusion criterion may be disregarded when conducting studies with healthy non-pregnant, non-lactating females, who are candidates for hormonal contraception.
21822019 ³⁸ , March 22, 2018	A statistical analysis plan (SAP), describing the planned analysis in detail as per the provisions in the PSG for Amneal’s adhesion study (Protocol # 16-VIN-0236) was submitted.	The request has been forwarded to protocol review queue. No further review is available.

Pre-ANDA meeting requests:

The Agency has not received any pre-ANDA meeting requests referencing the RLD/RS product.

Citizen petitions:

There are no pending citizen petitions currently.

Assessment:

To obtain an insight on the amount of EE that is being released in vivo from the applied RLD, RS and Test (Amneal) products and decipher the contribution of the application site (abdomen vs back) to the systemic exposure PK profile observed following application of the RLD, RS and Test (Amneal) product, dermal PBPK models were developed for the RLD, RS and the Test (Amneal) product using the Multi phase-multi layer (MPML) MechDermA module within Simcyp Simulator v19.

³⁷ <https://panorama.fda.gov/task/view?ID=5c18231a001ebbd76515986fc75f539d>

³⁸ <https://panorama.fda.gov/project/view?ID=5ab8fa880087b5096b67e3063057eb36>

The objective of developing and applying these models was to describe in a quantitative manner the absorption and disposition of EE in the different skin layers and the systemic circulation resulting from the application of the RLD, RS and Test product on the abdomen and back of healthy virtual subjects.

A systemic disposition model to characterize the systemic distribution and elimination of EE was developed initially and later coupled with a skin model to describe the permeation of EE through the skin layers following patch application. The model development and validation process are outlined below. Literature sources and information on the products of interest captured in NDA 021180, ANDA 200910, ANDA 213950 and other regulatory submissions were taken into consideration for model development and validation purposes.

Development of an EE systemic disposition model:

The physicochemical properties of EE on the molecular weight, $\log P_{o/w}$, pK_a , solubility, melting point, blood-to-plasma ratio and fraction unbound in the plasma were obtained from the literature or assumed.

The model was developed to describe the systemic disposition of EE based on literature data. To develop a mathematical model that describes the systemic disposition of EE, NDA 21180 and literature sources^{39,40,41} were utilized. Initial pharmacokinetic analysis on the EE PK data was conducted in the Simcyp Simulator v19. A minimal PBPK model was selected and the PK model parameter values used for building the systemic disposition model are provided below:

Table 8: EE physicochemical parameters and PK characteristics used for the development of the systemic disposition model.

Systemic disposition model		
Parameter	Value	Source
molecular weight (g/mol)	296.4	Pubchem ⁴²
Log $P_{o/w}$	3.67	Pubchem, Drugbank
pK_a 1/2	10.33/13.1 (diprotic acid)	Pubchem, Drugbank
Melting point	142-144°C	Pubchem, Drugbank
Water solubility	11.3 mg/L (at 27°C)	Pubchem, Drugbank

³⁹ Contraception. 1987 Oct;36(4):471-9. Comparative Pharmacokinetics of Levonorgestrel and Ethinylloestradiol Following Intravenous, Oral and Vaginal Administration. D J Back, S F Grimmer, S Rogers, P J Stevenson, M L Orme.

⁴⁰ NDA 021180, Clinical pharmacology review, Reviewer: Dhruva J Chatterjee, PhD, date: 11/16/2001.

⁴¹ Clin Pharmacol Ther. 2018 Dec;104(6):1229-1239. Risk-Benefit Assessment of Ethinylestradiol Using a Physiologically Based Pharmacokinetic Modeling Approach. Udoamaka Ezuruike, Helen Humphries, Maurice Dickins, Sibylle Neuhoff, Iain Gardner, Karen Rowland Yeo.

⁴² <https://pubchem.ncbi.nlm.nih.gov/compound/5991>

Blood/plasma ratio	1	Assumed ⁴³
Fraction unbound in plasma (f_u), albumin	0.015	Pubchem, Drugbank ⁴⁴
EE minimal PBPK model		
$V_{sac}/K_{in}/K_{out}/V_{ss}$ (L/Kg) (CV%)	2/0.287/0.096/4 (30)	Ezuruike et al.,2018 ⁴⁵
Elimination (in vivo clearance, CL_{iv} (L/h))	17 (30)	Pubchem, Drugbank

Performance assessment of the systemic disposition model:

The performance of the model was assessed leveraging observed data (plasma EE concentrations) following the administration of a single intravenous EE dose from two different sources; a literature report by Back et al., 1987⁴⁶ and the NDA 021180, Clinical pharmacology review⁴⁷ where the sponsor administered EE intravenously. No other dataset on intravenous administration of EE is available in the literature or in any regulatory submissions to the knowledge of this reviewer. The outcomes of the performance assessment are presented in **Figure 7** below.

⁴³ Clin Pharmacol Ther. 2018 Dec;104(6):1229-1239. Risk-Benefit Assessment of Ethinylestradiol Using a Physiologically Based Pharmacokinetic Modeling Approach. Udoamaka Ezuruike, Helen Humphries, Maurice Dickins, Sibylle Neuhoff, Iain Gardner, Karen Rowland Yeo.

⁴⁴ <https://www.drugbank.ca/drugs/DB00977#reference-A191182>

⁴⁵ Clin Pharmacol Ther. 2018 Dec;104(6):1229-1239. Risk-Benefit Assessment of Ethinylestradiol Using a Physiologically Based Pharmacokinetic Modeling Approach. Udoamaka Ezuruike, Helen Humphries, Maurice Dickins, Sibylle Neuhoff, Iain Gardner, Karen Rowland Yeo.

⁴⁶ Contraception. 1987 Oct;36(4):471-9. Comparative Pharmacokinetics of Levonorgestrel and Ethinylestradiol Following Intravenous, Oral and Vaginal Administration. D J Back, S F Grimmer, S Rogers, P J Stevenson, M L Orme.

⁴⁷ NDA 021180, Clinical pharmacology review, Table 25, Reviewer: Dhruva J Chatterjee, PhD, date: 11/16/2001.

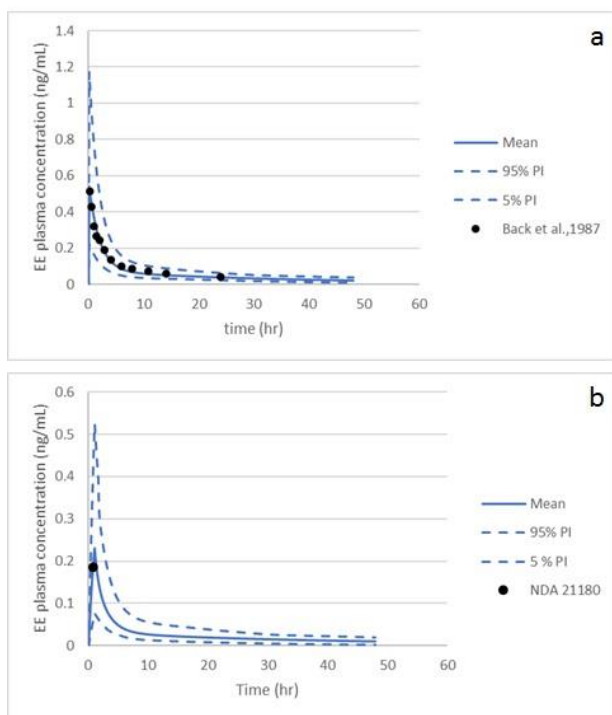


Figure 7: Observed (solid black) versus predicted (blue solid line is mean and blue dashed lines are 5 and 95% prediction intervals) PK profile of EE following single intravenous administration per Back et al.,1987 (a) and NDA 021180, Study NRGEEP-PHI-014⁴⁸ (b).

Overall, the performance of the systemic disposition model was considered acceptable.

The developed model was used for further modeling the absorption through the skin of ORTHO EVRA® TDS (NDA 021180), XULANE® TDS (NDA 200910) and the generic TDS developed by Amneal.

Development of the dermal PBPK model for EE formulated in several TDSs:

The dermal PBPK model was developed following a “bottom-up” approach leveraging the QSAR models embedded within the MPML MechDermA module for predictions on partitioning between skin layers and diffusivity within the different skin layers. To inform model parameters, to optimize several model parameters and assess the performance of the model literature sources, data from NDA 021180 and ANDAs 200910, 213950, and 213977 were utilized.

The skin physiology model component developed for dermatological drug products containing EE is presented below:

⁴⁸ NDA 021180, Clinical pharmacology review, Table 25, Reviewer: Dhruva J Chatterjee, PhD, date: 11/16/2001.

Table 9: Model parameter values (partition and diffusion coefficients) for the dermal PBPK model developed for EE applied as a dermatological product.

Dermal model, MPML MechDerma model, partition and diffusion coefficients		
Parameter	Value	Source
$K_{sp,SClip:veh}$	403.8	Predicted, QSAR model from Nitsche 2006 ⁴⁹
$K_{sp,SC:VE}$	0.1	Optimized ⁵⁰ from 4.28 by Shatkin and Brown ⁵¹
$K_{sp,sebum:veh}$	35533	Predicted, QSAR model from Valiveti ⁵²
$K_{sp,subcutis:dermis}$	10	Assumed based on the relative lipophilicity of EE
$K_{sp,blood:subcutis}$	0.1	Assumed based on the relative lipophilicity of EE
$K_{sp,dermis:VE}$	1	Assumed, similar physiology between dermis and VE
$K_{sp,dermis:blood}$	2.80	Predicted, QSAR model from Shatkin and Brown ⁵³
$K_{sp,dermis:sebum}$	0.0064	Predicted (unknown method or QSAR model)
$K_{sp,muscle:subcutis}$	0.1	Assumed based on the relative lipophilicity of EE
$K_{sp,blood:muscle}$	1	Assumed, similar handling of the two tissues considering the relative lipophilicity of EE
D_{SClip}	$1.49 \cdot 10^{-5}$	Predicted, QSAR model from Mitragotri 2003 ⁵⁴
D_{VE}	0.005	Optimized ⁵⁵ from 0.0001948 (QSAR model by modified Chen 2015)
$D_{subcutis}$	0.0005	Assumed, similar to D_{SClip}
D_{dermis}	0.005	Optimized ⁵⁶ from 0.0001948 (QSAR model by modified Chen 2015)
D_{sebum}	0.000525741	Predicted, QSAR model from Johnson et al., 1996 ⁵⁷

⁴⁹ Nitsche JM, Wang TF, Kasting GB. A two phase analysis of solute partitioning into the stratum corneum. J Pharm Sci 2006; 95(3): 649-666.

⁵⁰ Please, see Appendix

⁵¹ Shatkin JA, Brown HS. Environ Res. 1991; 56:90-108

⁵² Valiveti S, Wesley J, Lu GW. Investigation of drug partition property in artificial sebum. Int J Pharm. 2008;346(1-2):10-6.

⁵³ Shatkin JA, Brown HS. Environ Res. 1991; 56:90-108

⁵⁴ Mitragotri S. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. J Control Release. 2003 Jan 9;86(1):69-92.

⁵⁵ Please, see Appendix

⁵⁶ Please, see Appendix

⁵⁷ Johnson ME, Berk DA, Blankschtein D et al. Lateral diffusion of small compounds in human

D_{muscle}	0.0002	Assumed, similar handling of the relative lipophilic EE by dermis, VE and muscle
$P_{\text{corneocyte}}$	$1.0 \cdot 10^{-5}$ cm/h	Default. Not impactful based on sensitivity analysis.

Table 10: Model parameter values related to protein binding for the dermal PBPK model developed for EE applied as a dermatological product.

Dermal model, MPML MechDerma model, protein binding		
Parameter	Value	Source
$F_{u,SC}$, steady state	0.088	Predicted, Polak et al., 2018 ⁵⁸
$F_{u,dermis}$	0.015	Assumed to be the same as systemic circulation
$F_{u,subcutis}$	0.015	Assumed to be the same as systemic circulation
$F_{u,muscle}$	0.015	Assumed to be the same as systemic circulation

The formulation model component developed for dermatological drug products containing EE is presented below.

The MechDerma model provides several capabilities in modeling drug release from TDS. These include:

1. Dermal patch<Empirical release<Zero Order Release Rate: API is released from the patch at a fixed amount per hour (mg/hr). The fixed amount is defined by the user.
2. Dermal patch<Diffusion based release kinetics< Matrix: Higuchi release kinetics is assumed here⁵⁹. The diffusion of the API is estimated based on the vehicle molar volume, the vehicle viscosity and the volume fraction of the polymer. The solubility of the API in the polymer is also used as model input. The release rate is estimated based on the equation: Higuchi release rate = $2 \cdot \sqrt{((\text{initial concentration} \cdot \text{solubility in vehicle} \cdot \text{diffusion coefficient})/2)}$ ⁶⁰. Assumptions per Paul, 2011: a. “there is negligible resistance in the surrounding fluid to mass transfer of solute away from the matrix surface”, b. “...the rate at which the drug dissolves into the matrix from the particles must be much more rapid than the diffusional processes. “, c. (specific to the membrane-matrix composites) “...drug suspension in a fluid or gel phase where the drug loading far exceeds its solubility in this medium. Thus, the dissolved drug

stratum corneum and model lipid bilayer systems. Biophysical Journal 1996; 71(5):2656- 2668.

⁵⁸ Polak S, Mendky A, Patel N. Combining machine learning and mechanistic modelling approaches to solve real life problems-assessment of the local tissue binding and its influence on systemic exposure after topical application of drugs. ACoP9 San Diego, USA 2018

⁵⁹ Adv Drug Deliv Rev.2001 Jun 11;48(2-3):159-72. Modeling Transdermal Drug Release. Y N Kalia, R H Guy.

⁶⁰ Personal communication with Simcyp/Certara development team (Tariq Abdulla).

concentration remains constant during most of the delivery of drug from the system ... except for the initial burst and the final depletion phase.”

3. Dermal patch<Empirical release<Controlled Release: the user in inputting a profile of “% release over time” which indicates the % of initial amount loaded in the patch to be released following zero order kinetics by the indicated time.

Based on preliminary analysis, EE release from the patch post-application was better described by the Empirical release<Controlled Release model. Implementation of the different drug release models is described and discussed in detail in the Appendix. In brief, an advantage of the empirical release model is that it allows for predicting the in vivo drug release profile by leveraging in vivo PK profiles (systemic exposure) that are drug product-specific and assuming zero order (constant) release rate. The matrix release model considered drug release to be driven by the loaded dose of the API following Higuchi kinetics which did not seem to be appropriate in this case. Finally, the zero-order release model provided a less than ideal description of the observed data and overall did not provide with the flexibility of the controlled release model while making the same assumption of zero order release.

Development and validation of the abdomen, a new application site within the MechDerma model:

The MPML MechDerma model (b) (4) offers several application sites including back, face (cheek), forehead, upper arm, upper and lower leg. However, abdomen is not one of the offered application sites. As such, literature sources were leveraged towards informing physiology characteristics for abdomen.

The “back’ application site was utilized for building the abdomen application site under the assumption that all skin physiology parameters between the two application sites are the same except certain key ones that were updated. The skin physiology parameters within the “back” application site that were updated to capture the abdomen physiology are listed in the table below.

Table 11: Model parameter values related to the abdomen application site developed within the MechDerma model.

Dermal model, MPML MechDerma model, abdomen application site		
Parameter	Value (CV%) males/females	Source
Stratum corneum, skin surface pH	5.29 (10%)/5.98 (10%)	Bailey et al.,2012 ⁶¹

⁶¹ Lasers Surg Med. 2012 Feb;44(2):131-42. The Use of Non-Invasive Instruments in Characterizing Human Facial and Abdominal Skin. Steven H Bailey, Georgette Oni, Spencer A Brown, Natalie Kashafi, Salim Cheriyan, Michael Maxted, Collin Stewart, Caroline Jones, Patrick Maluso, Ashley M Kenkel, Matthew M Kenkel, John Hoopman, Fritz Barton Jr, Jeffrey M Kenkel.

Viable epidermis, thickness (µm)	99.8 (50%)	Wei et al., 2017 ⁶² , Table 2
Dermis, thickness (µm)	2284 (50.1%)	Wei et al., 2017, Table 2
Subcutis, thickness (µm)	17 (30%)/22 (30%)	Derraik et al., 2014 ⁶³ , Lancerotto et al., 2011 ⁶⁴
Muscle, thickness (µm)	8 (30%)/4 (30%)	Tanah et al., 2016 ⁶⁵

Based on Wei et al., 2017, Table 2, stratum corneum thickness was found to be 17.07 µm which is what is utilized as stratum corneum thickness for the “back” and was maintained while developing the abdomen as an application site.

Performance assessment for dermal PBPK models developed for EE RLD and RS TDS and validation of the abdomen, an application site developed within the MechDermA model:

ORTHO EVRA®: The NDA 021180 holder conducted a number of in vivo studies to support their drug development program and the NDA 021180 submission^{66, 67}. The list of studies includes:

- Study NRGEEP-PHI-014: randomized, parallel-group, open-label, two-way crossover study to evaluate the bioavailability of NGMN (also referred to as 17d-NGM) and EE from a transdermal contraceptive system versus intravenous infusion in 26 adult females. Each subject wore one ORTHO EVRA® on either the *abdomen or the buttock* (randomized) for 7 days, or they received a single intravenous infusion, 252 µg of 17d-NGM and 25 µg of EE over a 1-hour period (1 mL/min). One month after receiving the first treatment, they crossed over to the other treatment. *[Reviewer’s note: PK data (full PK profile) are not available for this study. As such, this study was not considered in the present report.]*
- Study NRGEEP-PHI-013: in this study, 24 healthy women were

⁶² Sci Rep. 2017 Nov 21;7(1):15885. Allometric Scaling of Skin Thickness, Elasticity, Viscoelasticity to Mass for Micro-Medical Device Translation: From Mice, Rats, Rabbits, Pigs to Humans. Jonathan C J Wei, Grant A Edwards, Darren J Martin, Han Huang, Michael L Crichton, Mark A F Kendall.

⁶³ PLoS One. 2014 Jan 21;9(1) Effects of Age, Gender, BMI, and Anatomical Site on Skin Thickness in Children and Adults With Diabetes. José G B Derraik, Marius Rademaker, Wayne S Cutfield, Teresa E Pinto, Sheryl Tregurtha, Ann Faherty, Jane M Peart, Paul L Drury, Paul L Hofman.

⁶⁴ Surg Radiol Anat. 2011 Dec;33(10):835-42. Layers of the Abdominal Wall: Anatomical Investigation of Subcutaneous Tissue and Superficial Fascia. Luca Lancerotto, Carla Stecco, Veronica Macchi, Andrea Porzionato, Antonio Stecco, Raffaele De Caro.

⁶⁵ J Physiol Anthropol. 2016 Aug 23;35(1):17. Measurement of Superficial and Deep Abdominal Muscle Thickness: An Ultrasonography Study. Nahid Tahan, Khosro Khademi-Kalantari, Mohammad Ali Mohseni-Bandpei, Saeed Mikaili, Alireza Akbarzadeh Baghban, Shapour Jaberzadeh.

⁶⁶ NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruva J. Chatterjee, Ph.D, date: 11/16/01.

⁶⁷ Fertil Steril. 2002 Feb;77(2 Suppl 2): S3-12. Pharmacokinetic Overview of Ortho Evra/Evra. Larry S Abrams, Donna Skee, Jaya Natarajan, Frankie A Wong.

studied with multiple doses of the EVRA patches for three consecutive weeks per cycle for three cycles. Additionally, volunteers were randomized to apply the patches either to the *abdomen* or the *buttocks*. The study is publicly available by Abrams et al., 2001⁶⁸. [Reviewer's note: *Contrary to Study NRGEEP-PHI-004/ Abrams et al., 2002*⁶⁹ discussed below, *Study NRGEEP-PHI-013/ Abrams et al., 2001*⁷⁰ showed that following single application and multiple patch applications, systemic exposure was higher when the patches were applied on the abdomen than the buttock. However, this was not a crossover design study.]

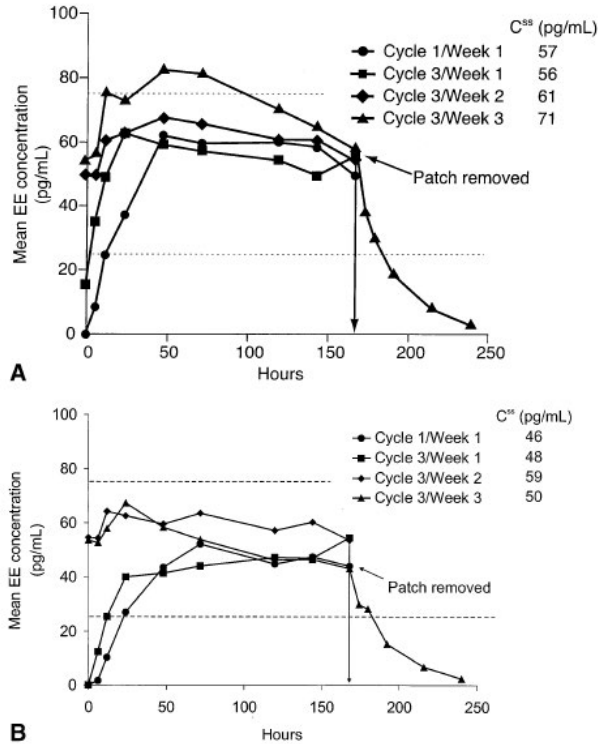


Fig. 2. (a) Mean serum concentration versus time profile of EE following patch application on the abdomen for three consecutive cycles. (b) Mean serum concentration versus time profile of EE following patch application on the buttock for three consecutive cycles. Horizontal dashed lines indicate upper and lower limits of reference range for EE.

Figure 8: Mean EE plasma concentration versus time PK profiles for study NRGEEP-PHI-013, NDA 021180 reported by Abrams et al., 2001.

68 Contraception. 2001 Nov;64(5):287-94. Multiple-dose Pharmacokinetics of a Contraceptive Patch in Healthy Women Participants. L S Abrams, D M Skee, J Natarajan, F A Wong, K C Lasseter.

69 Br J Clin Pharmacol 2002 Feb;53(2):141-6. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinylloestradiol at Four Application Sites. Larry S Abrams, Donna M Skee, Jaya Natarajan, Frankie A Wong, Gary D Anderson.

70 Contraception. 2001 Nov;64(5):287-94. Multiple-dose Pharmacokinetics of a Contraceptive Patch in Healthy Women Participants. L S Abrams, D M Skee, J Natarajan, F A Wong, K C Lasseter.

- Study NRGEEP-PHI-016⁷¹ is a BE study evaluating products between 2 manufacturers. [Reviewer's note: application site was not provided. As such, this study was not considered in the present report.]
- Study NRGEEP-PHI-004: a study focused to assess the effect of application of the patch at different anatomic sites on the absorption and PK of the drugs. Thirty-six healthy non-pregnant subjects wore one single patch for 7 days for each of the four treatment periods. Subjects were randomly assigned to wear the patch on the *abdomen, buttock, upper outer arm, or upper torso*. After a 1-month washout, subjects applied the patch at a different site alternately. Table 17 in the NDA 021180 in the Clinical Pharmacology Review⁷² summarizes the study outcomes. The study is publicly available by Abrams et al., 2002⁷³.

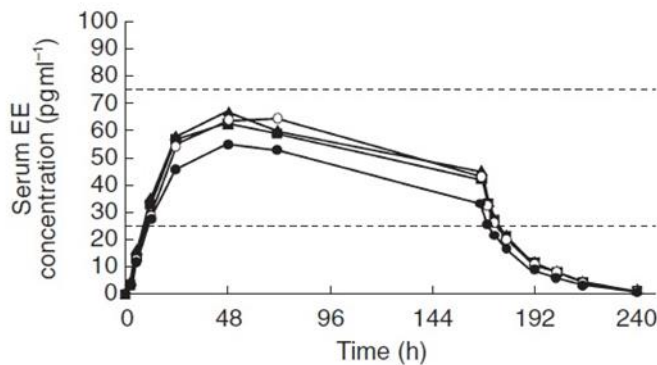


Figure 2 Mean serum concentration *vs* time profile of ethinyl oestradiol (EE) following successive applications of the contraceptive patch for 7 days at each of the four anatomical sites (● abdomen; ▲ arm; ■ buttock; ○ torso). Dashed horizontal lines indicate reference range.

Figure 9: Mean EE plasma concentration versus time PK profiles reported by Abrams et al., 2002.

- Study NRGEEP-PHI-015: a study to evaluate the PK parameters of 17d-NGM, progestin norgestimate (NGM), and EE following application of EVRA® when worn under conditions of heat, humidity, cold, and exercise as compared to the normal activity. Thirty healthy adult women, aged 19 to 47 years (mean = 32.7±7.65) and weighing 50.4 to 81.3 kg (mean = 64.1±8.32), were enrolled and 29 completed the study. Each subject wore a 20-cm² NGMN/EE EVRA® patch on the abdomen for 7 days under specified conditions during each of three treatment periods: each treatment

⁷¹ NDA 021180/S045, Biopharmaceutics review, Reviewer: Kelly Kitchens, PhD, date: 2/26/2014.

⁷² NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruba J. Chatterjee, Ph.D, date: 11/16/01.

⁷³ Br J Clin Pharmacol 2002 Feb;53(2):141-6. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinylloestradiol at Four Application Sites. Larry S Abrams, Donna M Skee, Jaya Natarajan, Frankie A Wong, Gary D Anderson.

period separated by a 1-month washout period. Once daily activities included: normal activity, sauna (10 minutes), whirlpool (10 minutes), cool water bath (up to 30 minutes), treadmill (20 to 30 minutes), and combination. The study is publicly available by Abrams et al., 2001⁷⁴. [Reviewer's note: Only the "normal activity" data were used in the present report.]

- Study NRGEEP-PHI-006: A randomized, open-label, single-center, three-way crossover study (# NRGEEP-PHI-006) was conducted to assess the dose proportionality of three sizes of the transdermal contraceptive system, namely 10 cm² (containing 3.0 mg 17d-NGM and 0.38 mg EE), 15 cm² (containing 4.5 mg 17d-NGM and 0.56 mg EE), and 20 cm² (containing 6.0 mg 17d-NGM and 0.75 mg EE). [Reviewer's note: application site was not provided. As such, this study was not considered in the present report.]
- Study NRGEEP-PHI-012: a study was conducted in 20 healthy adult women (age 18 to 48 years). Each subject wore a 20-cm² NGMN/EE EVRA® contraceptive patch on the abdomen for 1 week alone and for 1 week with coadministered tetracycline HCl (500 mg q.i.d. for 3 days prior to and 7 days during wear). A 1-month washout period separated the two-wear periods. [Reviewer's note: Only the "patch only" data were used in the present report.]

The formulation used in studies NRGEEP-PHI-012, -013, -014, -015, and -016 is the same as the proposed to-be-marketed formulation per the NDA 021180 Clinical pharmacology Review⁷⁵.

- Study NRGEEP-PO1-1026⁷⁶ (postapproval study): The primary objective of this study is to compare the PK of ORTHO EVRA® exhibiting faster equilibration profile with the PK of currently marketed ORTHO EVRA in healthy female volunteers, after application to the *buttock*. This was a single-center, randomized, open-label, 2-way crossover study. Healthy adult, non-pregnant women were randomized to wear either ORTHO EVRA® with a faster equilibration profile or currently marketed ORTHO EVRA® for 7 days during the open-label phase, washing out for 21 days and then crossing over to the other treatment for 7 days. Forty subjects were randomized. [Reviewer's note: Only the "currently marketed" data were used in the present report.]
- Study NRGEEP-PO1-121⁷⁷ (postapproval study): A BE study of a low cumulative release lot of ORTHO EVRA (LOW SPEC NGMN-EE) patches compared with currently marketed ORTHO EVRA® in healthy

⁷⁴ J Clin Pharmacol. 2001 Dec;41(12):1301-9. Pharmacokinetics of Norelgestromin and Ethinyl Estradiol Delivered by a Contraceptive Patch (Ortho Evra/Evra) Under Conditions of Heat, Humidity, and Exercise. L S Abrams, D M Skee, J Natarajan, F A Wong, P T Leese, G W Creasy, M M Shangold.

⁷⁵ NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruba J. Chatterjee, Ph.D, date: 11/16/01.

⁷⁶ NDA 021180 (Serial # 017), Clinical Pharmacology and Biopharmaceutics Review, Reviewer: Christy S. John, Ph.D, date: 7/25/05.

⁷⁷ NDA 021180 (Serial # 017), Clinical Pharmacology and Biopharmaceutics Review, Reviewer: Christy S. John, Ph.D, date: 7/25/05.

female volunteers. The goal of this study was to assess the BE of NGMN/EE transdermal contraceptive system from LOW SPEC NGMN-EE compared with currently marketed ORTHO EVRA® contraceptive system after application to the *buttock*. This was a single center, randomized, double blind, 2-way crossover study. The double-blind treatment phase included two 7-day treatment periods separated by 28-day washout period. Forty female subjects were randomly assigned to 1 of 2 treatment sequence groups. *[Reviewer’s note: Only the “currently marketed” data were used in the present report.]*

- Study NRGEEP-PO1-1024⁷⁸ (postapproval study): a multicenter, open-label, randomized, partially-balanced, incomplete block design study evaluating the exposure rates across 13 commercial lots of ORTHO EVRA® compared with clinical development Lot 01607 of ORTHO EVRA®. Non-pregnant, non-lactating, nonsmoking, healthy subjects with a history of regular menstrual cycles, were included. Thirteen manufactured lots, representing 10% of the overall commercial lots, were selected for this study and were considered to be sufficient to descriptively evaluate the hormone delivery across lots. Eligible subjects were randomly assigned to 1 of 26 treatment-sequence groups. Each of the ORTHO EVRA® patches from 1 of the 13 lots was applied to the *buttock* of each subject and worn for 7 days.

The clinical PK (mean PK profiles) data described above and utilized for this report are presented in the **Figure 10** below. The mean PK profile obtained for the RLD within the context of in vivo BE study ORTH-0942 supporting ANDA 200910 (please, see below for a complete description of the study) is also provided. Variability associated with the systemic PK of EE following the ORTHO EVRA® TDS application is noted as well as the higher exposure observed with the product under ANDA 200910, study ORTH-0942. Due to that variability, a clear definition of systemic PK among the different application sites when the clinical PK data is considered in its totality may be challenging, contrary to what was reported in NDA 021180, Study NRGEEP-PHI-004/ Abrams et al., 2002⁷⁹.

⁷⁸ NDA 021180, Clinical Pharmacology and Biopharmaceutics Review/Consult, Reviewer: Stephan Ortiz, date: 11/22/2005.

⁷⁹ Br J Clin Pharmacol 2002 Feb;53(2):141-6. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinyloestradiol at Four Application Sites. Larry S Abrams, Donna M Skee, Jaya Natarajan, Frankie A Wong, Gary D Anderson.

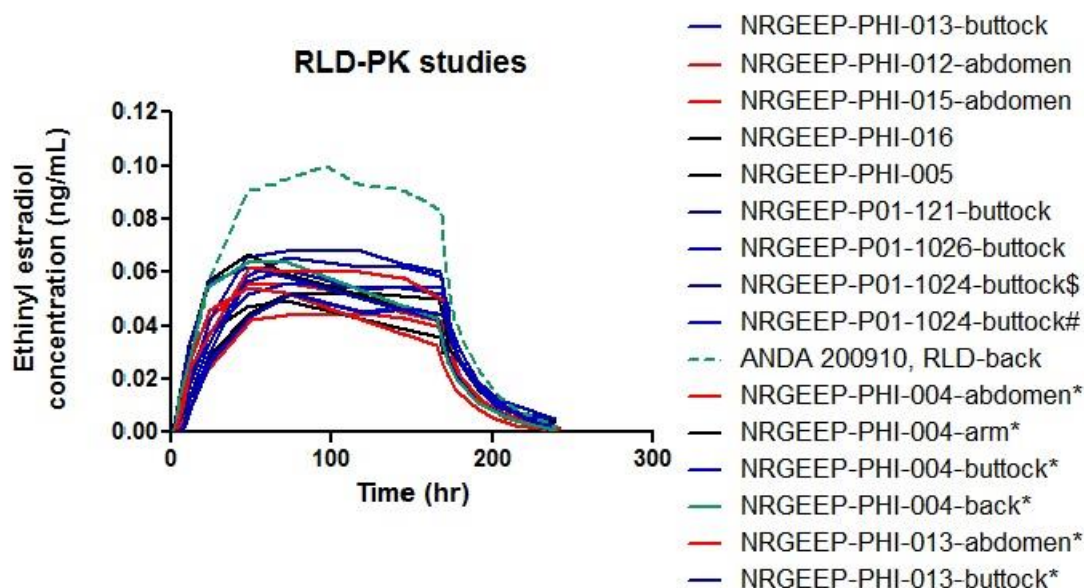


Figure 10: Mean EE plasma concentration versus time PK profiles for studies supporting NDA 021180 and ANDA 200910. *Data extracted from the literature, \$: clinical lot, #: commercial lot. All data were extracted from single dose studies, NRGEEP-PHI-013 data were from Cycle 1, Week 1 (C1W1). Application sites are color-coded: Back in green, abdomen in red, buttock in blue, arm in black.

Leveraging the validated back physiology already available within the MechDerma model, the in vivo % drug release profile for EE following the application of ORTHO EVRA® TDS on the back of study participants was predicted by performing deconvolution. This was a challenging task considering the variability observed on the PK of EE following the application of the ORTHO EVRA® TDS as shown on [Figure 10](#). Therefore, deconvolution efforts focused on generating simulated PK profiles that describe the clinical PK data from ANDA 200910, RLD-back and NRGEEP-PHI-004-back (Abrams et al., 2002) documented on [Figure 11](#).

The obtained deconvoluted % drug release profile is provided on the [Table 12](#) below:

Table 12: Predicted in vivo EE release profile for the RLD obtained leveraging the product-specific dermal PBPK model and clinical PK data from ANDA 200910, RLD-back and NRGEEP-PHI-004-back (Abrams et al., 2002).

Time post TDS application	50h	75h	168h
% EE Release	9	12.5	25.5

% Release represents the percentage of initial EE loaded amount release up to the respective time point. Zero order release is assumed throughout the entire wear period (0 to 168 hours).

The obtained deconvoluted % drug release profile suggests that by the end of the application period (at t=168 hr post-application), 25.5% of the loaded amount is delivered which would equal to $0.255 * 750 \mu\text{g} = 191.3 \mu\text{g}$ of ethinyl estradiol. The model-predicted delivery for the RLD (25.5%) is notably lower than the % delivery estimated based on the residual drug analysis (61.5%, Table 1). Figure 11 provides the model-predicted PK profile (mean and 95/5% prediction intervals) following product application on the back which described the observed data reasonably well. The simulated population comprised of 20 females, 20 to 40 years of age, that applied the patch on their back for 7 days to resemble the overall population/study design observed in the relevant clinical trials.

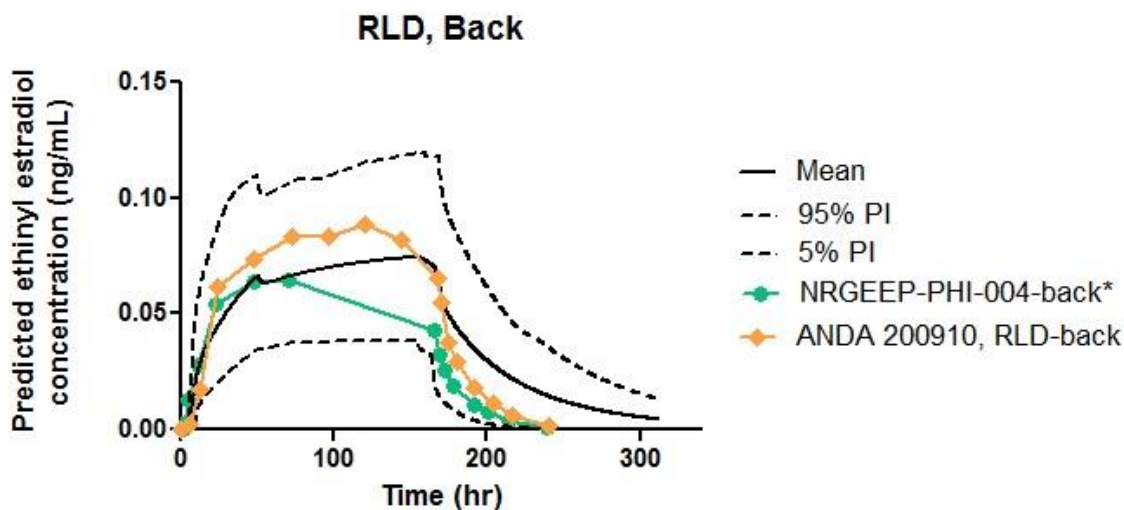


Figure 11: Observed (solid) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the back of (virtual) healthy female volunteers. Observed data are for BE study supporting ANDA 200910 and NDA 021180, Study NRGEEP-PHI-004/Abrams et al., 2002.

To validate the abdomen skin physiology as an application site developed by the reviewer within the MechDermA model, the previously validated dermal PBPK model for ORTHO EVRA® TDS application on the back (Figure 11) was leveraged towards predicting systemic exposure for the same product following patch application on the abdomen. The model-generated mean PK profile (95/5% prediction intervals) is provided in the Figure 12 below against observed PK profiles. The model predictions on systemic exposure following patch application on the abdomen described the observed data well. This outcome increased confidence in the developed abdomen physiology within the MechDermA model and contributed to the overall validation of the abdomen as an application site.

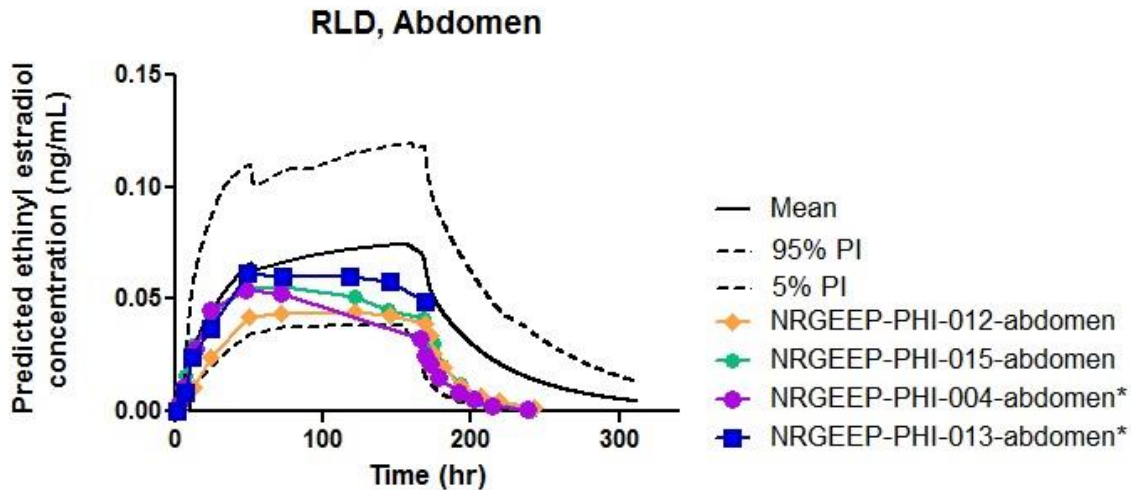


Figure 12: Observed (solid) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the abdomen of (virtual) healthy female volunteers. Observed data are studies NRGEEP-PHI-012/015 supporting NDA 021180 and studies reported in the literature Study NRGEEP-PHI-004/Abrams et al., 2002 and NRGEEP-PHI-013/Abrams et al., 2001.

Further validation of the abdomen physiology implementation under single application and multiple patch applications was conducted leveraging clinical PK data from Study NRGEEP-PHI-013 where model predictions were compared to observed PK data collected following single dose (Cycle 1, Week 1) and repeated patch applications (Cycle 3, Week 1/2/3). The results of this validation exercise are presented on **Figure 13**.

NDA 021180, Study NRGEEP-PHI-013

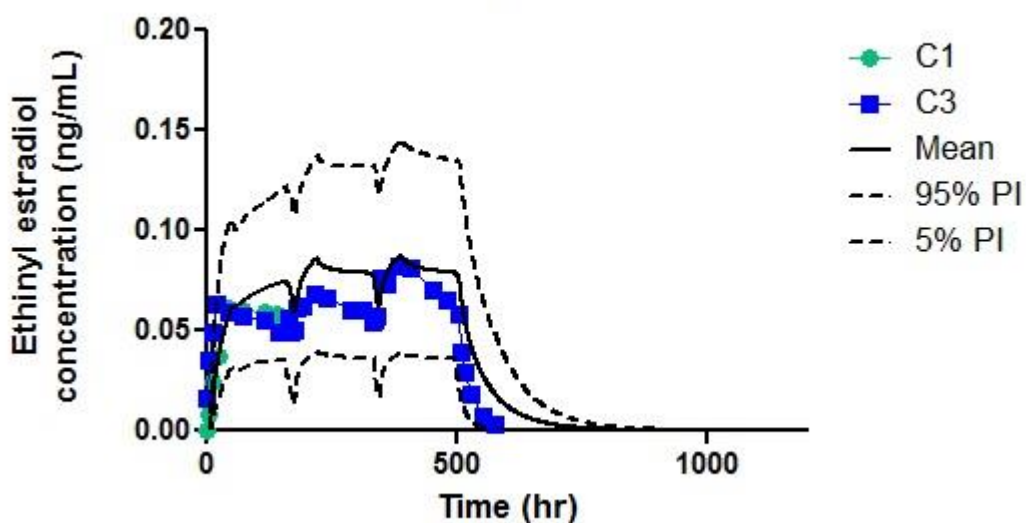


Figure 13: Observed (solid) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following multiple application of the RLD on the abdomen of (virtual) healthy female volunteers. Observed data is study NRGEEP-PHI-013 supporting NDA 021180, C1: cycle 1, Cycle 3. Data from C1 are from week 1 and C3 are from week 1/2/3.

The abdomen physiology implementation along with the capability of the MechDermA model to model expected proportionality in the delivery of EE from patches of differing areas of application and loaded drug amounts was conducted leveraging clinical PK data from Study NRGEEP-PHI-006 where model predictions were compared to observed PK data collected following single application of patches of 10 cm² (containing 3.0 mg NGMN and 0.38 mg EE), 15 cm² (containing 4.5 mg 17d-NGM and 0.56 mg EE), and 20 cm² (containing 6.0 mg 17d-NGM and 0.75 mg EE) for 7 days. The results of this validation exercise are presented on **Figure 14**.

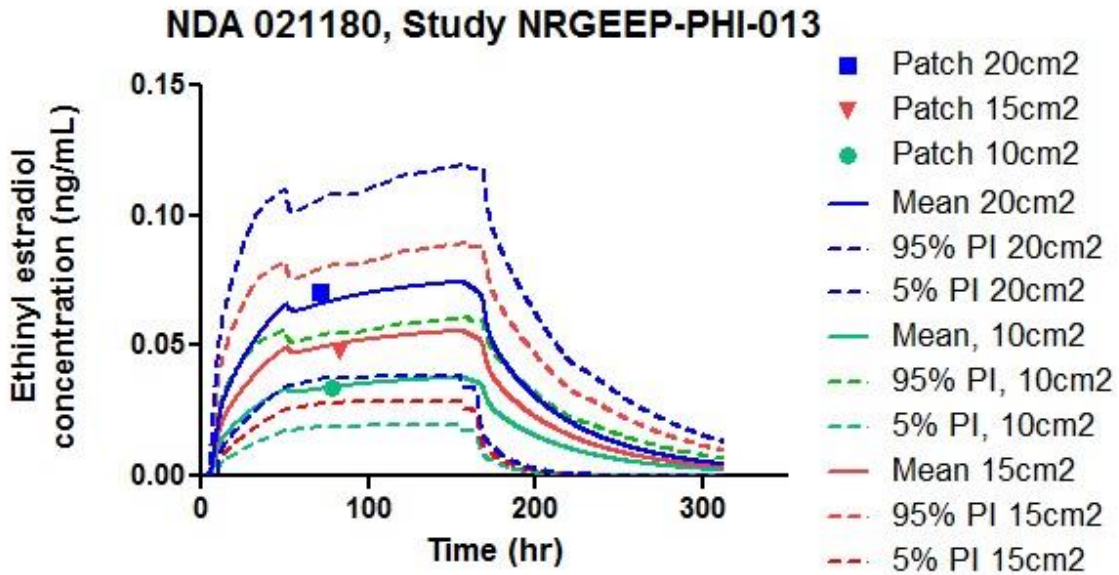


Figure 14: Observed (solid) versus predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the abdomen of (virtual) healthy female volunteers. Observed data is from study NRGEEP-PHI-006 supporting NDA 021180.

A comparison of the model-generated predictions following application on the back versus the abdomen for the ORTHO EVRA® TDS is provided below showing similarity in predicted PK profiles.

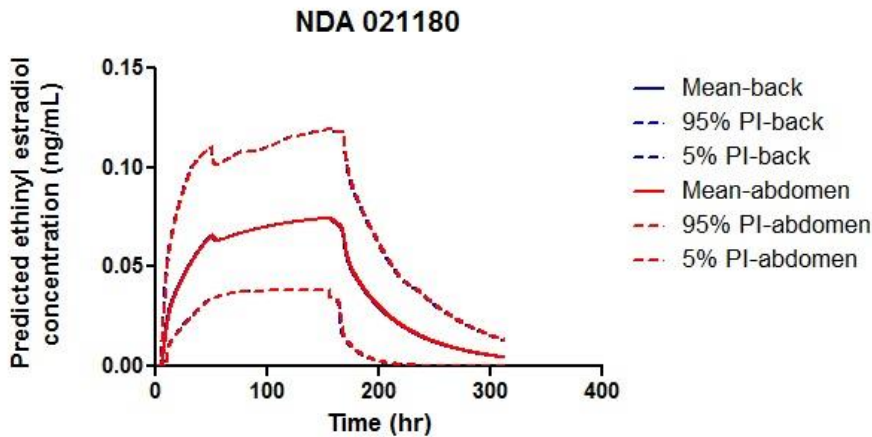


Figure 15: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the abdomen (red) or the Back (blue) of virtual healthy female volunteers. The simulated population was 20 females, 20 to 40 years of age that applied the patch for 7 days.

XULANE®: The ANDA 200910 holder (Mylan Technologies Inc) conducted the pivotal in vivo BE study ORTH-0942⁸⁰ to demonstrate BE between their test product XULANE and ORTHO EVRA®. The table below summarizes the study design and study outcomes; the TDS was applied on the back of the study participants. Per the review by DB⁸¹, the two products were found to be BE.

Table 13: Summary of pivotal in vivo BE study ORTH-0942 supporting ANDA 200910.

Study Ref. No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (range))	Mean Parameters (+/-SD)						Study Report Location
					Cmax (pg/mL)	Tmax (hr)	AUCt (pg*hr/mL)	AUCi (pg*hr/mL)	tHalf (hr)	kel (1/hr)	
Study No: ORTH-0942	Bioequivalence Study of Norelgestromin and Ethinyl Estradiol Transdermal System (NEETS) Patch (0.15 mg/0.02 mg/day; Mylan) and Ortho Evra® Patch (0.15 mg/0.02 mg/day; Ortho) in Normal Healthy Female Volunteers	Open-Label, Single-Dose, Randomized, Two-Period, Two-Treatment Crossover, bioequivalence study	Test (T): Norelgestromin and Ethinyl Estradiol Transdermal System, 0.15 mg/0.02 mg/day × 7 days [Batch No: R6A0014] Mfg Date: Dec 2010	21 Healthy Female subjects Age: 24 (19-35)	Ethinyl Estradiol						Section 5.3.1.2
			Reference (R): Ortho Evra® 0.15 mg/0.02 mg/day × 7 days Film (norelgestromin and ethinyl estradiol) [Lot No.: 7LM5212] Expiry Date: March 2013		99.59 (±24.11)	120 (48-170)	12853.9 (±2669.8)	12996.8 (±2701.3)	17.29 (±3.45)	0.0417 (±0.0085)	
					111.0 (±27.42)	96 (48-168)	14948.1 (±3244.2)	15108.5 (±3252.8)	17.02 (±2.58)	0.0417 (±0.0065)	

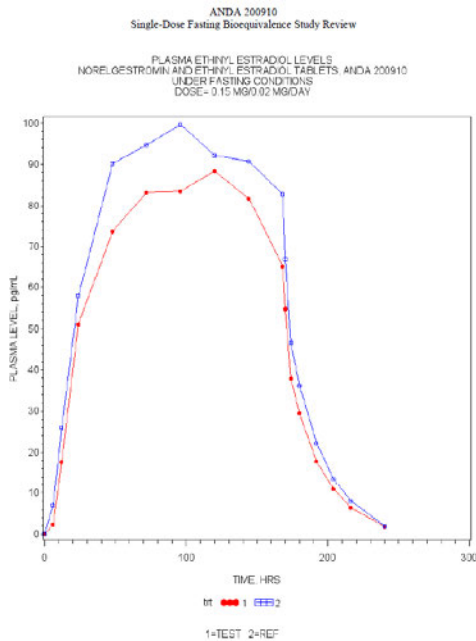


Figure 16: Mean EE PK profiles for Test (RS) and Reference (RLD) products from the pivotal in vivo BE study ORTH-0942 supporting ANDA 200910.

⁸⁰ ANDA200910, ANDA200910-ORTH-0942 Clinical Report.pdf

⁸¹ ANDA 200910, Division of Bioequivalence Review, Reviewer: Suman Dandamudi. Date: 06/05/2013.

XULANE® was utilized for BE assessments under ANDA 213950 (current product) and ANDA 213977 (pending ANDA as of 06/20/2020, submitted by Teva Pharmaceuticals). For both pending ANDAs, the TDS was applied on the abdomen in the pivotal PK BE studies. The currently available PK profiles for the RS XULANE® are presented in **Figure 17** below:

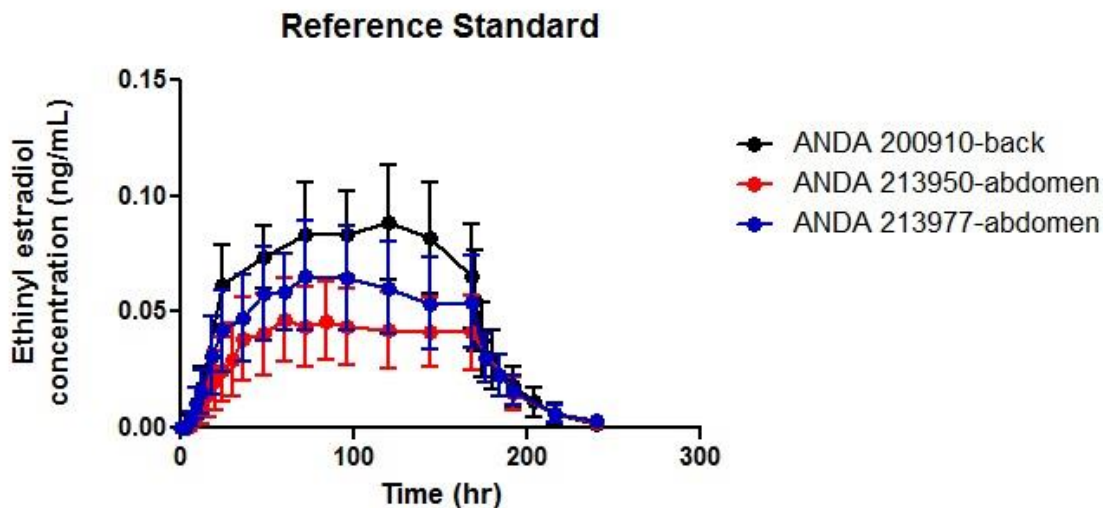


Figure 17: Mean ($\pm$ SD) EE plasma concentration versus time PK profiles for studies supporting ANDA 200910 (application on back), ANDA 213950 and 213977 (application on abdomen) following application of the RS. ANDA 213950 and 213977 are currently under review (not approved).

Leveraging the validated back physiology already available within the MechDerma model and the mean PK profile for EE obtained from ANDA 200910, study ORTH-0942, the % drug release profile for EE following the application of XULANE® TDS on the back of study participants was predicted by performing deconvolution. The deconvoluted % drug release profile that was obtained is provided in **Table 14** below.

Table 14: Predicted in vivo EE release profile for the RS obtained leveraging the product-specific dermal PBPK model and clinical PK data from ANDA 200910, study ORTH-0942.

Time post TDS application	50h	75h	168h
% EE Release	16	23	42

% Release represents the percentage of initial EE loaded amount release up to the respective time point. Zero order release is assumed throughout the entire wear period (0 to 168 hours).

The deconvoluted % drug release profile suggests that by the end of the application period (at t=168 hr post-application), 42% of the loaded amount is delivered which would equal $0.42 * 530 \mu\text{g} = 223 \mu\text{g}$. The model-predicted delivery for the RS (42%) is notably lower than the % delivery estimated based on

the residual drug analysis (70%, Table 1). Figure 18 provides the model-predicted PK profile (mean and 95/5% prediction intervals) following product application on the back described the observed data reasonably well. The ANDA 200910, study ORTH-0942 population/design was considered in the simulation (21 females, 19-35 years of age, application of the patch for 7 days on the back).

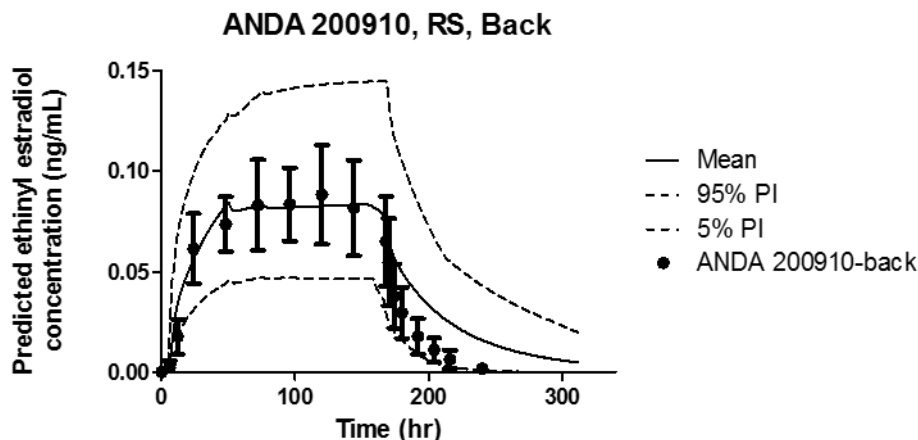


Figure 18: Observed (solid) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RS on the back of (virtual) healthy female volunteers. Observed data are for BE study supporting ANDA 200910.

To validate the abdomen as an application site (developed by the reviewer) within the MechDermA model, the previously validated dermal PBPK model for XULANE® TDS application on the back (Figure 18) was leveraged towards predicting systemic exposure for the same product following patch application on the abdomen. The model-generated mean PK profile (95/5% prediction intervals) is provided in the Figure 19 below against observed PK profiles. The model predictions on systemic exposure following patch application on the abdomen described the observed data well. This outcome increased confidence in the developed abdomen physiology within the MechDermA model and contributed to the overall validation of the abdomen as an application site.

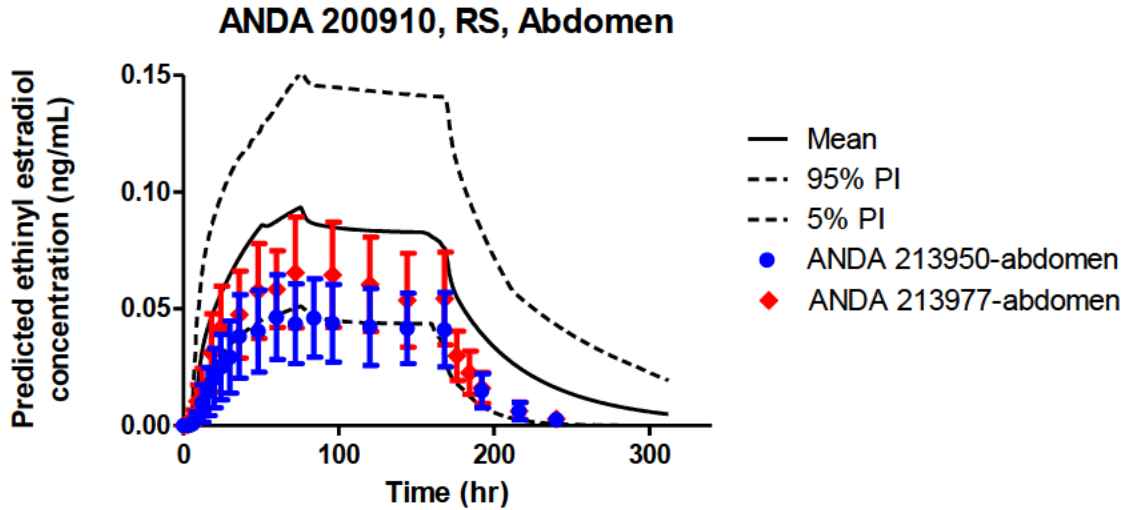


Figure 19: Observed (solid) versus predicted (black solid line is mean and black dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RS on the abdomen of (virtual) healthy female volunteers. Observed data are in vivo BE studies supporting ANDA 213950 (blue) and ANDA 213977 (red). ANDA 213950 and 213977 are current under review (not approved).

A comparison of the model-generated predictions following application on the back versus the abdomen for the XULANE® TDS are provided below showing no difference between the two application sites (Figure 20).

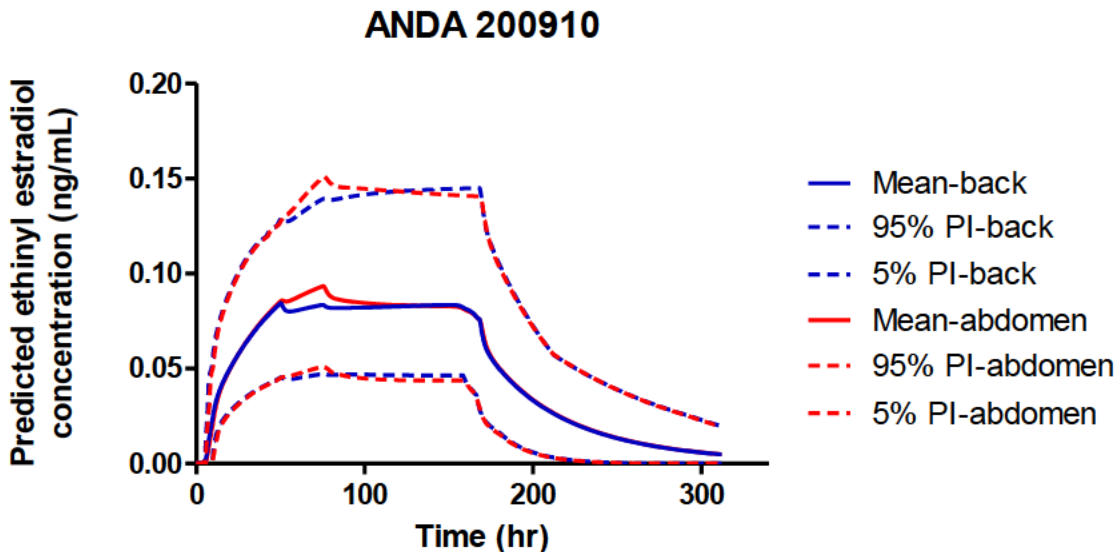


Figure 20: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RS on the abdomen (red) or the back (blue) of virtual healthy volunteers. The simulated

population was 20 females, 20 to 40 years of age that applied the patch for 7 days.

Performance assessment for dermal PBPK models developed for EE released from RS and Test TDS (ANDA 213950) and estimation of the EE drug release profiles for the RS and Test TDS (ANDA 213950):

Amneal NGMN and EE TDS under ANDA 213950: The applicant conducted the pivotal in vivo BE study ESTN/2018/1607 to demonstrate BE between their generic TDS and the RS XULANE®. This study has been summarized previously.

Test product:

Leveraging the validated abdomen physiology within the MechDerma model, the PK profile for EE was predicted (mean and 95/5% prediction intervals). The ESTN/2018/1607 study population/design was considered in the simulation (79 females, 24-31 years of age, application of the patch for 7 days on the abdomen). The model prediction is presented below on **Figure 21**. The model-predicted PK profile following product application on the abdomen described the observed data reasonably well.

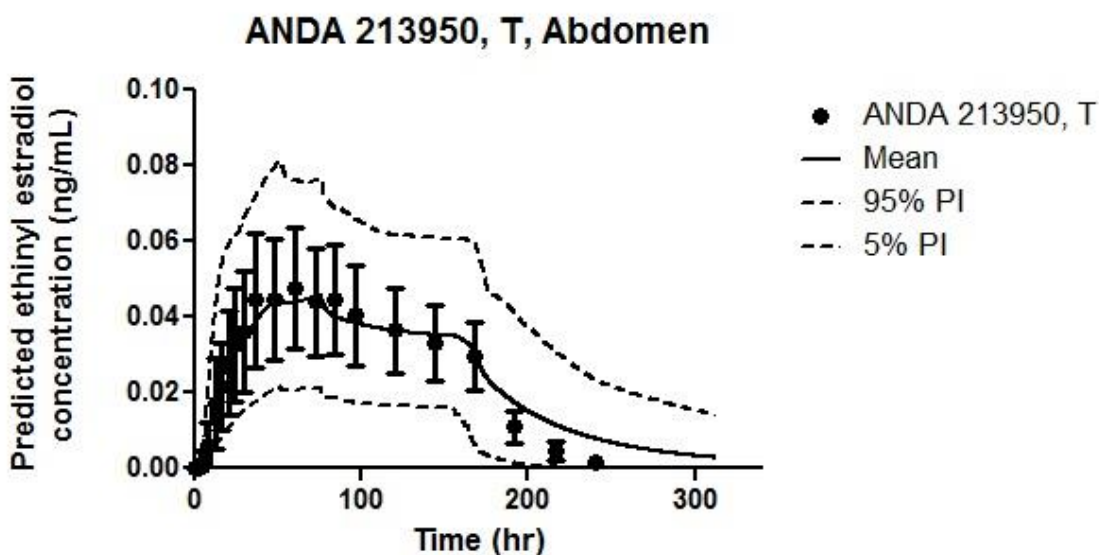


Figure 21: Observed (solid) versus predicted (black solid line is mean and black interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test product on the abdomen of (virtual) healthy female volunteers. Observed data are in vivo BE study supporting ANDA 213950. Simulations conditions matched the ones of the in vivo study supporting ANDA 213950.

The % drug release profile deconvoluted from the PK data is provided in **Table 15**.

Table 15: Predicted in vivo EE release profile for the T obtained leveraging the product-specific dermal PBPK model and clinical PK data from ANDA 213950, study ESTN/2018/1607.

Time post TDS application	50h	75h	168h
% EE Release	16	22	38

% Release represents the percentage of initial EE loaded amount release up to the respective time point. Zero order release is assumed throughout the entire wear period (0 to 168 hours).

The deconvoluted % drug release profile suggested that by the end of the application period (at t=168-hour post-application), 38% of the loaded amount was delivered which would equal $0.38 * 289 \mu\text{g} = 109.8 \mu\text{g}$. This prediction is lower than the one obtained by the residual analysis where 52.25% of EE was determined to be delivered.

The validated dermal PBPK model for the Test product by Amneal (ANDA 213950) was leveraged towards predicting systemic exposure for the TDS following patch application on the back rather than the abdomen. The model-generated mean PK profiles (95/5% prediction intervals) is provided in the **Figure 22** below:

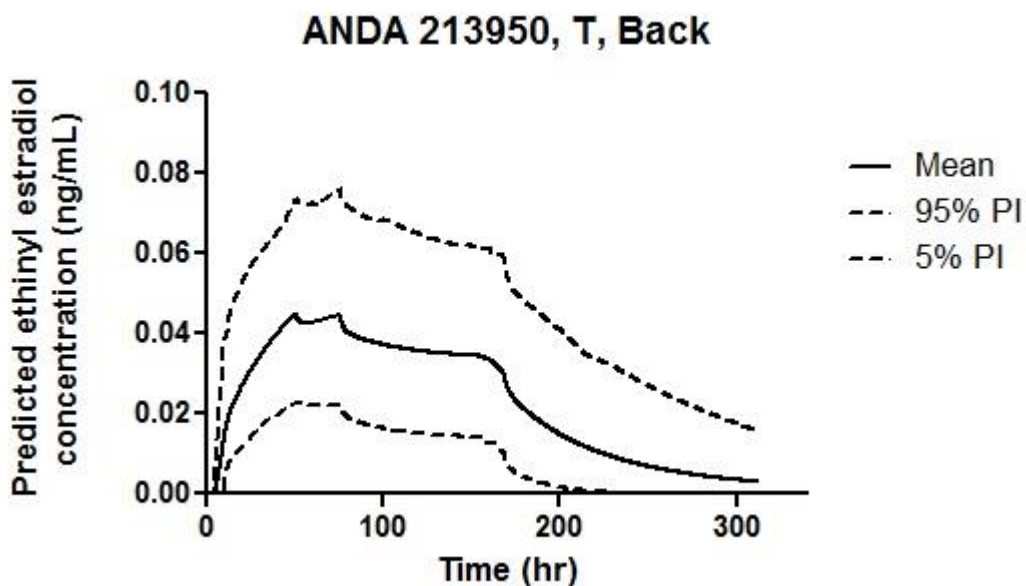


Figure 22: Predicted (black solid line is mean and black interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test product on the back of virtual healthy female volunteers. Simulation conditions matched the ones of the in vivo study supporting ANDA 213950.

A comparison of the model-generated predictions following application on the back versus the abdomen for the ANDA 213950, Test product are provided below showing no difference between the two application sites (Figure 23).

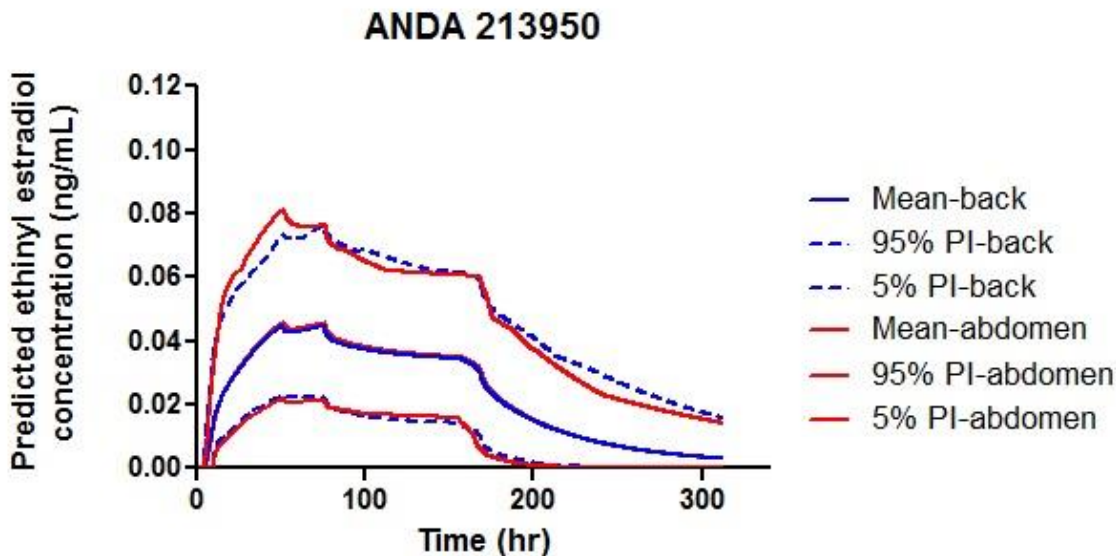


Figure 23: Predicted (solid line is mean and interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test product (ANDA 213950) on the abdomen (red) or the back (blue) of virtual healthy female volunteers. Simulations conditions matched the ones of the in vivo study supporting ANDA 213950.

Reference standard:

Leveraging the validated abdomen physiology within the MechDerma model, the PK profile for EE following the application of the RS product was predicted (mean and 95/5% prediction intervals). The ESTN/2018/1607 study population/design was considered in the simulation (79 females, 24-31 years of age, application of the patch for 7 days on the abdomen). The model prediction is presented below on Figure 24. The model-predicted PK profile following product application on the abdomen described the observed data reasonably well.

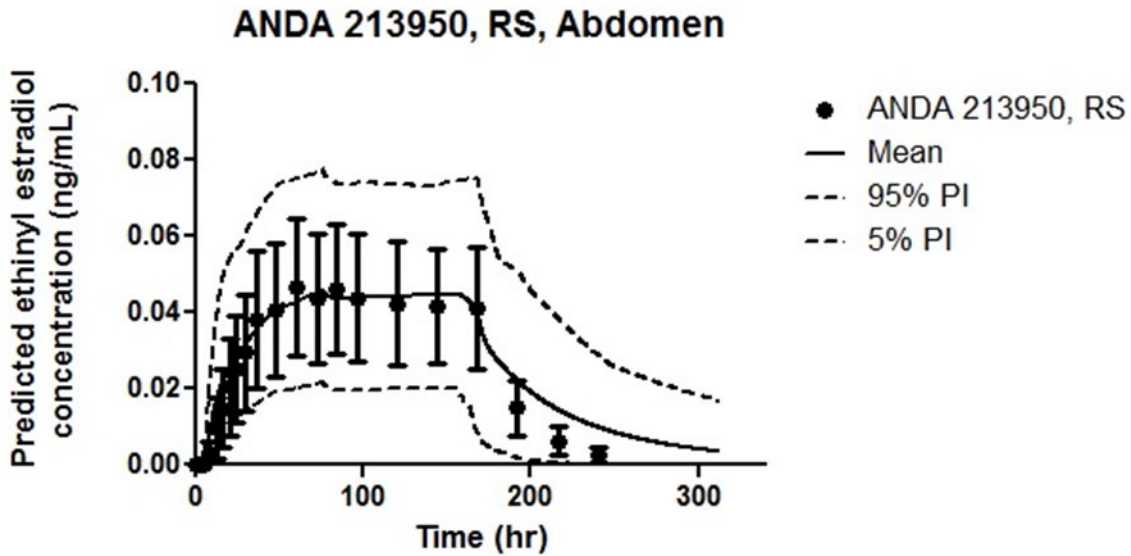


Figure 24: Observed (solid) versus predicted (black solid line is mean and black interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RS on the abdomen of (virtual) healthy female volunteers. Observed data are in vivo BE study supporting ANDA 213950. Simulations conditions matched the ones of the in vivo study supporting ANDA 213950.

Simulation conditions matched the ones of the in vivo study supporting ANDA 213950.

The % drug release profile deconvoluted from the PK data is provided in [Table 16](#).

Table 16: Predicted in vivo EE release profile for the RS product obtained leveraging the product-specific dermal PBPK model and clinical PK data from ANDA 213950, study ESTN/2018/1607.

Time post TDS application	50h	75h	168h
% EE Release	8	11.5	22

% Release represents the percentage of initial EE loaded amount released up to the respective time point. Zero order release is assumed throughout the entire wear period (0 to 168 hours).

The deconvoluted % drug release profile suggested that by the end of the application period (at t=168 hours post-application), 22% of the loaded amount was delivered which would be equal to $0.22 * 530 \mu\text{g} = 116.6 \mu\text{g}$ of EE. The model-predicted delivery (22%) is lower than the % delivery identified in ANDA 213950 (32.08%) and lower than the one estimated for ANDA 213977 (48.46%) and significantly lower than the one reported for ANDA 200910 (70.00%) for the RS.

The validated dermal PBPK model for the RS product (ANDA 213950) was leveraged towards predicting systemic exposure for the TDS following patch application on the back rather than the abdomen. The model-generated mean PK profiles (95/5% prediction intervals) is provided in the [Figure 25](#) below and overlaid against the mean predicted PK profile following application on the abdomen for the RS (ANDA 213950); no difference is observed between the two application sites.

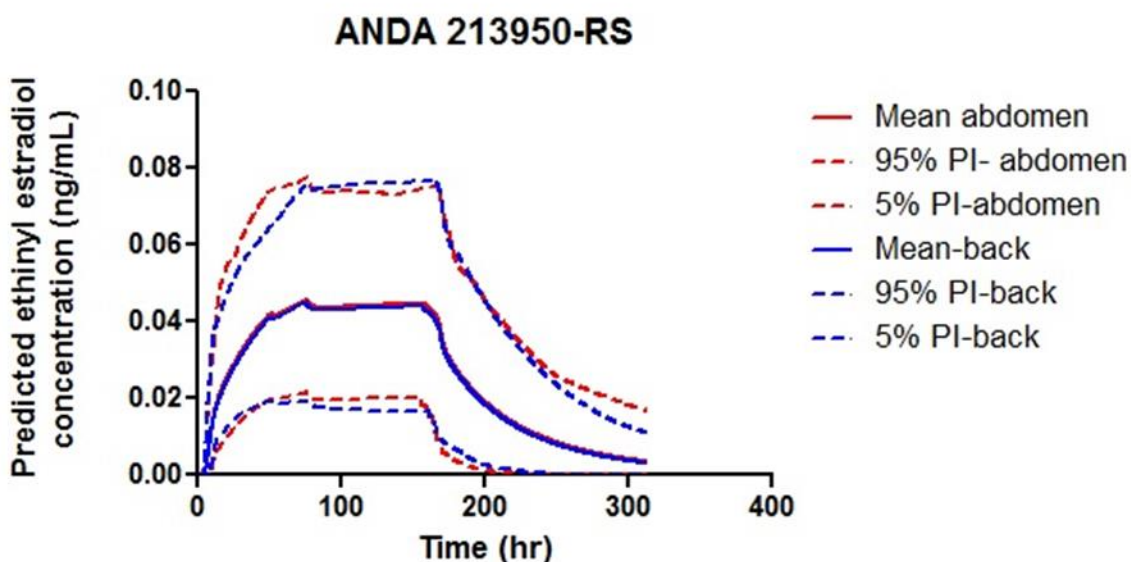


Figure 25: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RS (ANDA 213950) on the abdomen (red) or the back (blue) of virtual healthy female volunteers. Simulations conditions matched the ones of the in vivo BE study supporting ANDA 213950.

Despite of the lack of mechanistic basis in describing drug release when utilizing the empirical drug release model, excipient effects such as the ones induced by penetration enhancers are taken into account for the deconvolution of the systemic PK profiles under the assumption that they impact systemic exposure and are reflected in the % drug release profile.

Further quantifying these empirical release profiles allows one to decipher the impact of penetration enhancers and potentially obtain an insight on the performance of the patch in terms of release of drug during its wear time. [Table 17](#) below presents the amounts of EE released from the patch over 3 time periods of wear: 0 to 50 hours, 50 to 75 hours and 75 to 168 hours. These time periods were selected by visually inspecting the observed PK profiles obtained post-application of the patch; **in general**, across the majority of the available PK profiles across all three TDSs, EE plasma concentrations increased rapidly for the first 50 hours following patch application, the rate of increase decreased over the

next 50 to 75 hour period and EE plasma concentrations remained overall stable past 75 hours and until patch removal at 168 hours.

Table 17: Predicted EE cumulative amount released and predicted EE release rate for the RS (ANDA 213950) and Test (ANDA 213950) products obtained leveraging product-specific dermal PBPK models.

	Time Interval	Amount released (mg)	Release rate ($\mu\text{g}/\text{day}$)
Amneal	0-50 hr	0.046	22.2
	50-75 hr	0.064	16.6
	75-168 hr	0.110	11.9
RS	0-50 hr	0.042	20.4
	50-75 hr	0.061	17.8
	75-168 hr	0.117	14.4

A graphical representation of this data is provided below (Figure 26). The data suggested that in terms of amounts and release rates, the Test and RS products released EE at the same rate as the nominal release rate per the drug label for the first 50 hours. The EE release rate was similar to the one determined by the residual drug analysis for the Test product for the first 50 hours. However, although Test and RS continued to release EE at very similar rates and amounts up 75 hours, the Test product appeared to release slightly lower amounts of the API (at lower rates) which may in part explain the observed decrease in the EE plasma concentrations (Figure 6).

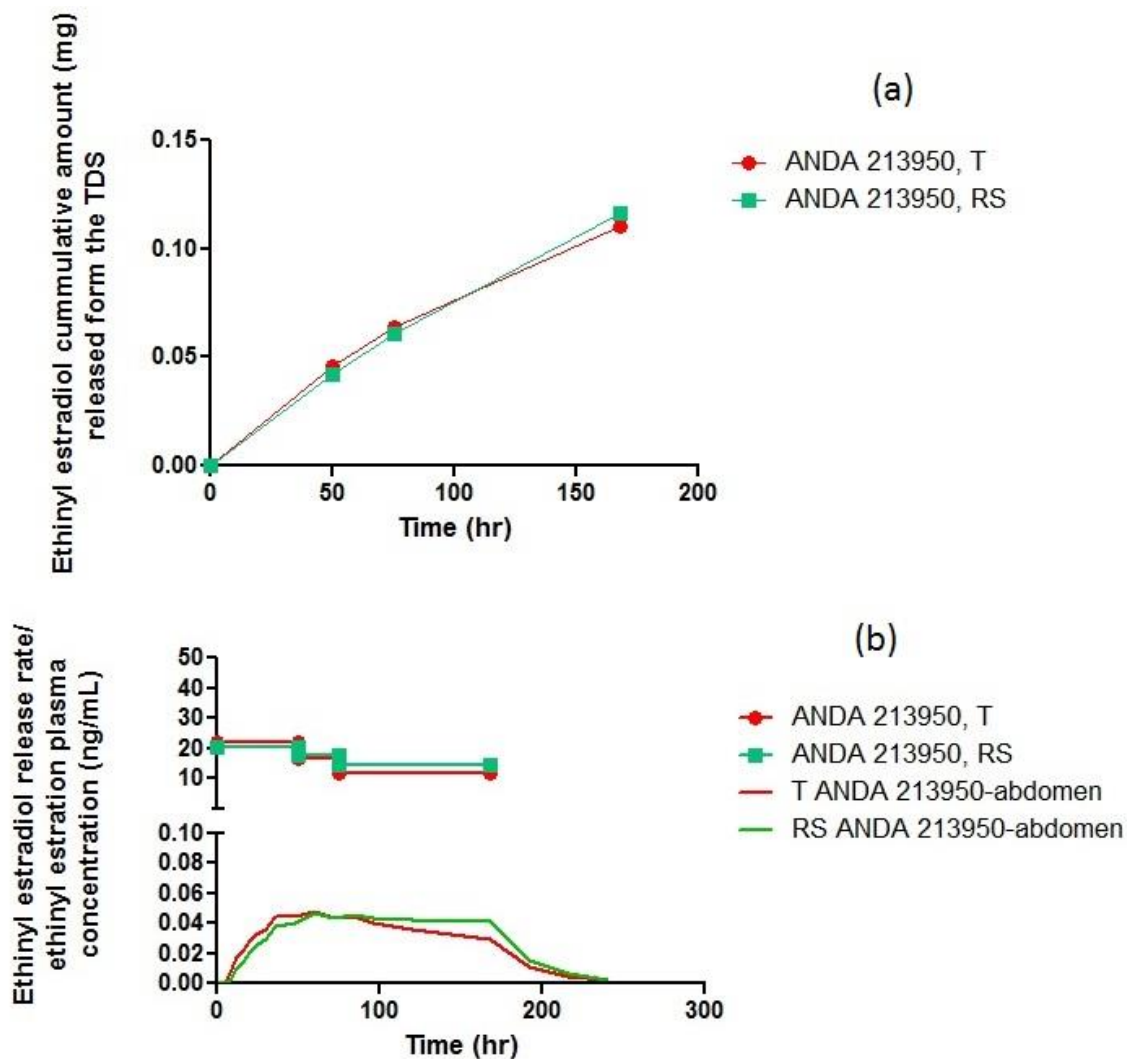


Figure 26: Predicted EE cumulative amount released (mg) (a) and predicted EE release rate ($\mu\text{g}/\text{day}$) (b) for the RS and Test (ANDA 213950) products obtained leveraging product-specific dermal PBPK models. EE release rates are assumed to be drug-product specific. EE PK profiles for RS and Test obtained in study ESTN/2018/1607 supporting ANDA 213950 are provided for comparison.

A residual drug/penetration enhancer study was conducted to support ANDA 213950⁸² titled: "A Comparative Residual Drug and Residual Enhancer analysis for Test Formulation of Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 μg per day by Amneal Pharmaceuticals and Reference standard (RS), XULANE® (Norelgestromin and Ethinyl Estradiol Transdermal System) 150/35 μg per day (Mylan Pharmaceutical Inc.) at the completion of delivery period." The Residual Enhancer amount of Oleyl Alcohol and Dipropylene glycol remaining on the used patches of Study # ESTN/2018/1607, Version # 01 was determined by gas chromatography (GC) technique. The lot of NGMN and EE TDS 150/35 μg per

⁸² ANDA 213950, Residual Drug and Residual Enhancer Study Report - ANDA213950, EDR, accessed 06/23/2020.

day used was Lot # PW-ST-18020A (Mfg Date: 10/02/2018). Study samples were analyzed for quantification of residual drug and residual enhancer using validated analytical methods.

The results of the penetration enhancer study are summarized in **Table 18** below.

Table 18: Amount of residual enhancer in the Test and the RS products at the end of the wear period of ANDA 213950, Study # ESTN/2018/1607.⁸³

7.4 Summary of Residual Enhancer results

Table 5. Amount of Residual Enhancer in Patch (mg)	
Product	(b) (4)
Test	(b) (4)
Reference	(b) (4)

Although the relative (b) (4) is higher in the Test product ((b) (4) %) compared to the RS ((b) (4) %), the residual analysis showed that about the same overall amount of this penetration enhancer was delivered over the wear period; 2.38 mg was delivered for the Test and 2.24 mg was delivered for the RS. In the case of (b) (4), this penetration enhancer accounts of (b) (4) % and (b) (4) % of the Test and the RS products, respectively. However, based on the residual analysis (b) (4) was the delivery rate for the Test product versus (b) (4) for the RS. **Table 19** below summarizes these findings.

Table 19: Calculated delivered amounts for the permeation enhancers (b) (4) (b) (4) for RS and Test (Amneal) products leveraging the residual drug and penetration enhancer analysis conducted for ANDA 213950.

Product	(b) (4)
Test (Amneal)	(b) (4)
Reference (RS)	(b) (4)

It may be reasonable to assume that the (b) (4) of penetration enhancers delivered in the skin for the Test product contributed and ensured that the initial delivery rate was comparable between the Test product and the RS despite of the difference in loaded EE amounts between the two products in in vivo BE study ANDA 213950, study ESTN/2018/1607. The increased local EE delivery for the Test compared to the RS product has also been observed in the in vitro skin permeation studies the applicant has performed (**Figure 5**).

⁸³ ANDA 213950, Residual Drug and Residual Enhancer Study Report - ANDA213950, EDR, accessed 06/23/2020.

Model predictions on systemic EE exposure following application of the RS or the Test product per ANDA 213950, study ESTN/2018/1607 are summarized in **Figure 27** below. Predicted PK profiles are predicted to be similar in shape and systemic exposure is predicted to be similar between the abdomen and back for the Test and the RS. Dose depletion is not predicted based on the model for any of the two products.

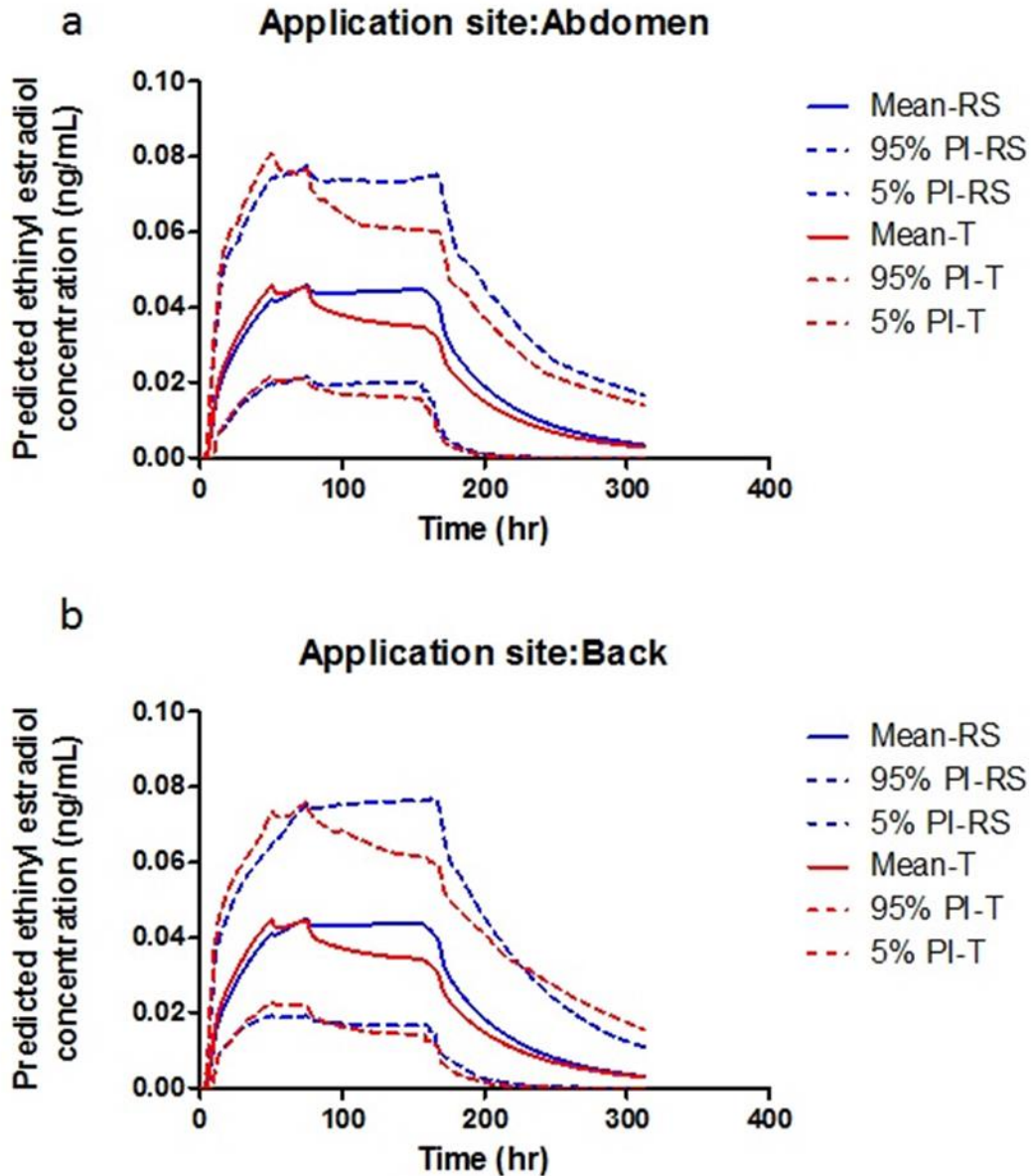


Figure 27: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test (T) and RS (ANDA 213950) on the abdomen (a) or the back (b) of virtual healthy female volunteers. Simulations conditions matched the ones of the in vivo BE study supporting ANDA 213950.

Model predictions on systemic EE exposure following application of the RS or the Test product per ANDA 213950, study ESTN/2018/1607 over a 21-day cycle (3 back-to-back patch applications) are summarized in **Figure 28** below. Predicted PK profiles are predicted to be similar in shape and systemic exposure is predicted to be similar between the Test and the RS.

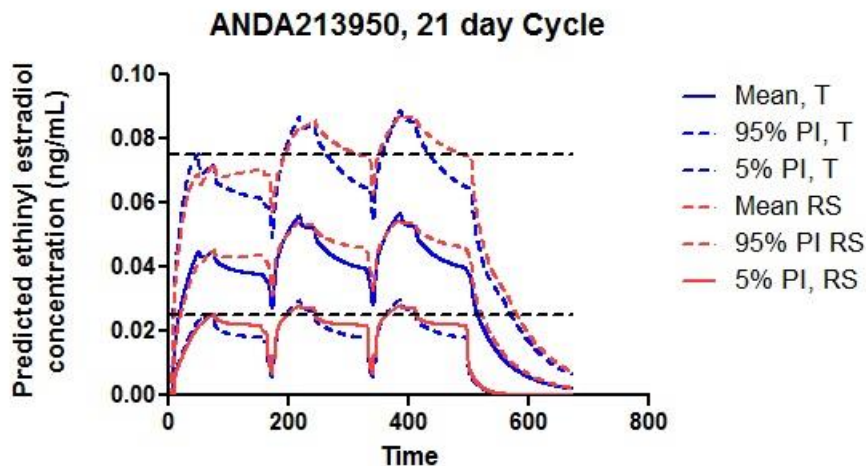


Figure 28: Predicted (solid line is mean and dashed lines are 5 and 95% prediction intervals) PK profile of EE following single application of the Test (T) (blue) and RS (red) on the abdomen of virtual healthy female volunteers. Simulations conditions matched the ones of the in vivo BE study supporting ANDA 213950. Dashed lines represent the targeted steady state concentration (C_{ss}) of EE 25-75 pg/mL per the NDA 021180 Clinical Pharmacology review.

Appendix:

Elimination of EE following the removal of the patch:

As shown in the main body of this consult (under “Assessment” section), systemic disposition of EE was well captured by the model following intravenous administration of EE in females. However, when the same model was used to predict the elimination of EE following removal of the patch, elimination from the systemic circulation was predicted to take place slower than observed in the clinical PK studies reported under NDA 021180, ANDA 200910 and ANDA 213950.

To improve the model predictions following the removal of the patch (at time 168 hours and onwards), sensitivity analysis was performed and showed that the stratum corneum (SC) to viable epidermis (VE) partition coefficient and the VE and dermis diffusion coefficients were model parameters impacting the rate of elimination from the systemic circulation. Modification (manual optimization) of these 3 parameters resulted in a decrease in the transit time of EE in the skin which essentially renders it readily available for elimination from the systemic circulation post-patch removal.

The improvement in the model predictions of the elimination of ethinyl estradiol from the systemic circulation post patch removal is shown in **Figure 29** below.

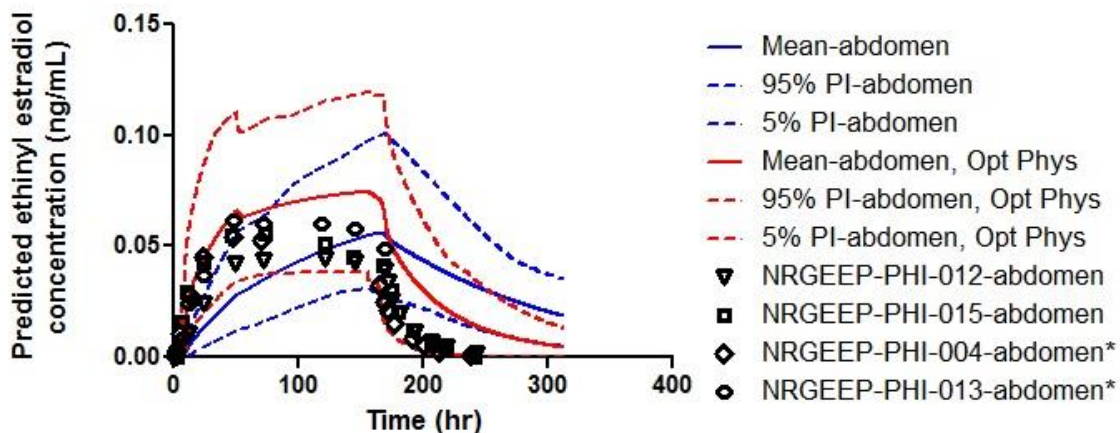


Figure 29: Observed (solid) versus predicted (solid line is mean and interrupted lines are 5 and 95% prediction intervals) PK profiles of EE following single application of the RLD product on the abdomen of (virtual) healthy female volunteers. Predictions were generated considering (red) and not considering (blue) optimizations in the skin physiology parameters of the developed models. Observed data are obtained from in vivo BE studies supporting NDA 021180. *Data from the literature.

However, when the optimized skin physiology was utilized to predict systemic PK profiles following patch application on the back and the abdomen, no difference

between those predicted PK profiles was noted. This absence of difference contradicted the difference observed in systemic PK profiles following application on the back versus the abdomen based on reported by a certain literature source where PK exposure following application on the back, buttock or arm is higher than PK exposure following patch application on the abdomen⁸⁴. The reviewer would like to note that this relationship was not verified in other literature reports where systemic PK profiles following patch application on the abdomen were higher than those obtained following application on the buttock of female subjects⁸⁵. The unclear relationship between application site and systemic PK exposure is evident in the NDA 21182 Clinical Pharmacology Review⁸⁶ and on **Figure 10** of this review.

Considering that:

1. the objective of the developed model for generic NGMN and EE TDS, 150/35 µg/day (Test, ANDA 213950) is to predict the total delivered amount of EE for the entire wear period for the RLD, RS and Test product. Skin and systemic disposition is critical in quantifying the delivered EE amount from the patch to the skin. Therefore, capturing systemic and skin disposition in the developed model is important,
2. the MechDermA model was validated towards describing systemic PK for EE following application of the RLD and RS on the back and abdomen of healthy female subjects,
3. There is no established relationship between application site and systemic EE PK based on contradicting literature reports and the NDA 21182 Clinical Pharmacology and Biopharmaceutics Review and in consideration of high variability observed with EE systemic PK.

it was decided to not proceed with the model where skin physiology was modified to better describe EE elimination from the systemic circulation. The limitation of not describing EE elimination from the systemic circulation by the proposed model is acknowledged as well as the fact that it does not directly impact any of the conclusions extracted from this PBPK modeling analysis.

Selection of appropriate drug release mechanism from the studied patch:

Several models of drug release are available within the MechDermA model. Their performance was evaluated here.

⁸⁴ Br J Clin Pharmacol 2002 Feb;53(2):141-6. Pharmacokinetics of a Contraceptive Patch (Evra/Ortho Evra) Containing Norelgestromin and Ethinylloestradiol at Four Application Sites. Larry S Abrams, Donna M Skee, Jaya Natarajan, Frankie A Wong, Gary D Anderson.

⁸⁵ Contraception. 2001 Nov;64(5):287-94. Multiple-dose Pharmacokinetics of a Contraceptive Patch in Healthy Women Participants. L S Abrams, D M Skee, J Natarajan, F A Wong, K C Lasseter.

⁸⁶ NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruva J. Chatterjee, Ph.D, date: 11/16/01.

1. Dermal patch < Empirical release < Zero Order Release Rate: the API is being released from the patch at a fixed amount per hour (mg/hr). The fixed rate is defined by the user.

Per the RLD label, EE is being delivered at a constant rate of 35 $\mu\text{g}/24$ hour or 1.46 $\mu\text{g}/\text{hour}$. Two different delivery rates were evaluated: 20 and 35 $\mu\text{g}/\text{day}$. The predicted profiles are provided in the **Figure 30** below. The predicted PK profiles do not agree with the observed PK profiles; the absorption phase is not well captured. Additionally, although a constant nominal release rate is assumed by the RLD, it is not expected that the in vivo EE release will be constant. As such, this model of drug release was not deemed acceptable although it has the potential of evaluating the potential for drug amount depletion as seen on **Figure 31**.

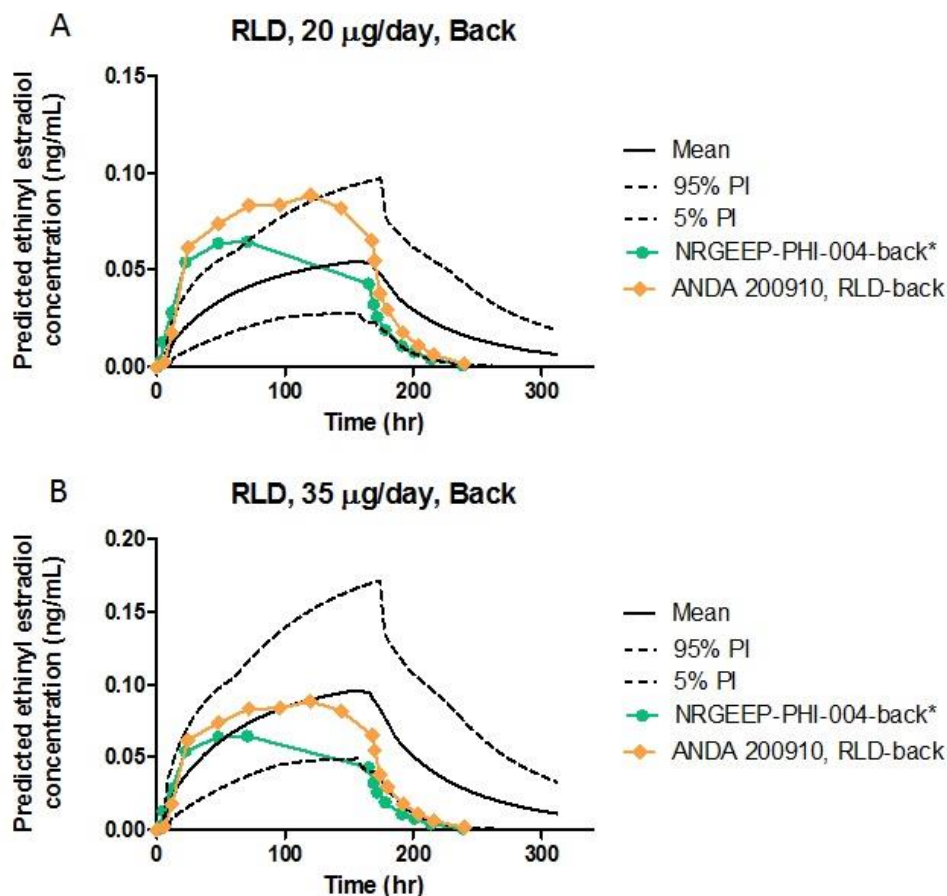


Figure 30: Observed (solid) versus predicted (black solid line is mean and black interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the back of (virtual) healthy female volunteers assuming a constant release rate equal to 20 $\mu\text{g}/\text{day}$ (A) and 35 $\mu\text{g}/\text{day}$ (B). Observed data are for BE study supporting ANDA 200910 and NDA 021180, Study NRGEEP-PHI-004/Abrams et al., 2002.

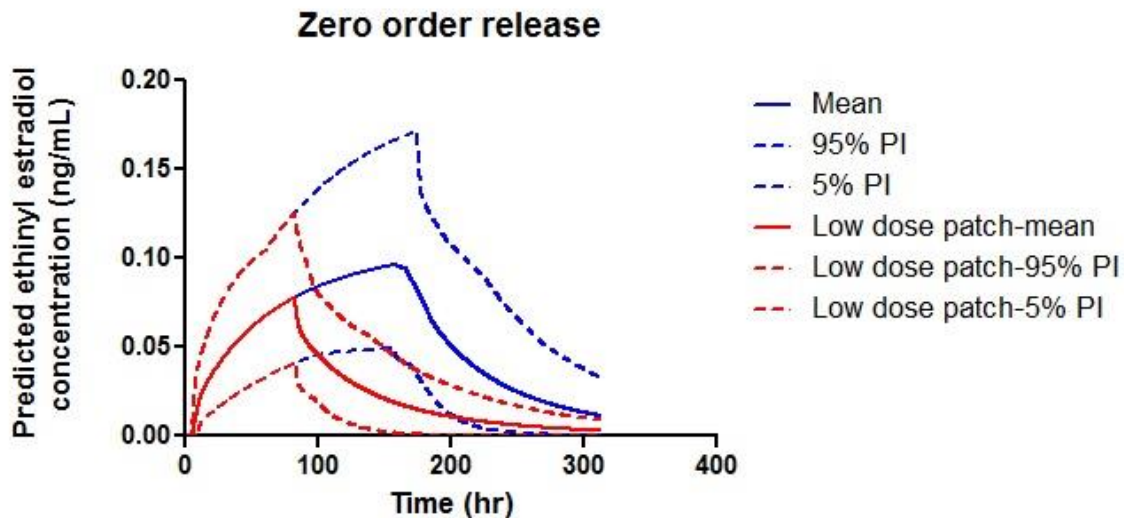


Figure 31: Predicted PK profiles (solid line is mean and black interrupted lines are 5 and 95% prediction intervals) of EE following single application of the RLD on the back of virtual healthy female volunteers assuming zero order release from the patch. Simulated loading doses were 0.75 mg (blue) which is the dose of the ORTHO EVRA® TDS and a lower dose 0.12mg selected to result in depletion following day 3 of application.

2. Dermal patch<Diffusion based release kinetics< Matrix: API is being released from the patch following the Higuchi equation⁸⁷. Assumptions per Paul, 2011⁸⁸: a. “there is negligible resistance in the surrounding fluid to mass transfer of solute away from the matrix surface”, b. “...the rate at which the drug dissolves into the matrix from the particles must be much more rapid than the diffusional processes. “, c. (specific to the membrane-matrix composites) “...drug suspension in a fluid or gel phase where the drug loading far exceeds its solubility in this medium. Thus, the dissolved drug concentration remains constant during most of the delivery of drug from the system ... except for the initial burst and the final depletion phase.”

The majority of these assumptions are not met in the current case of the EE patches that are modeled here. For instance, EE is fully dissolved in the patch and there are no API particles that may maintain the concentration gradient by constantly dissolving. Additionally, skin permeation is taking place while the skin is resisting API permeation, ie diffusion from the patch into the skin is not without resistance. Although these assumptions were not maintained in the present case, this drug release model was explored. The diffusion of the API within the model can be estimated based on the vehicle molar volume, the vehicle viscosity and the volume fraction of the

⁸⁷ Int J Pharm. 2011 Oct 10;418(1):13-7. Elaborations on the Higuchi Model for Drug Delivery. D R Paul.

⁸⁸ Int J Pharm. 2011 Oct 10;418(1):13-7. Elaborations on the Higuchi Model for Drug Delivery. D R Paul.

polymer. The solubility of the API in the polymer is also used as model input. The release rate is estimated based on the equation: Higuchi release rate = $2 \cdot \sqrt{((\text{initial concentration} \cdot \text{solubility in vehicle} \cdot \text{diffusion coefficient})/2)^{89}}$.

In the case of the studied patches, the vehicle molar volume cannot be estimated for the polymer utilized since the molecular weight of the polymer is not determined. As such, the diffusion of the API within the patch (D_{veh}) was not estimated by the software and had to be optimized. EE solubility in the polymer used in the patches studied here was obtained from the literature equal to 0.09 mg/mL^{90,91}. The Optimized D_{veh} value was $4 \cdot 10^{-5}$ cm²/h. The predicted PK profiles for the RLD following the optimization of D_{veh} are presented in Figure 32 below.

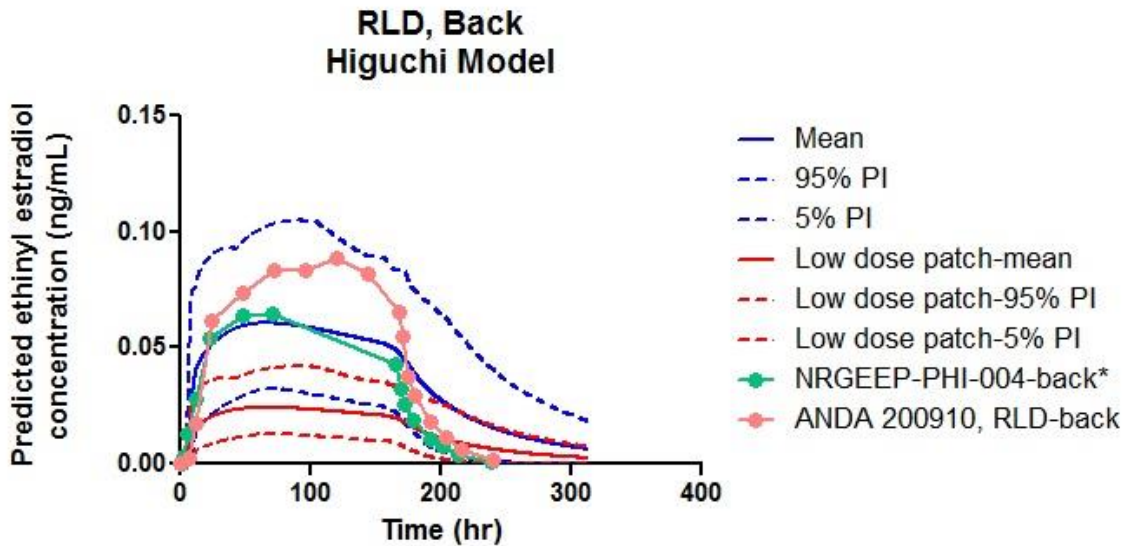


Figure 32: Observed (solid) versus predicted (black solid line is mean and black interrupted lines are 5 and 95% prediction intervals) PK profile of EE following single application of the RLD on the back of (virtual) healthy female volunteers assuming a Higuchi kinetic release model. Simulated loading doses were 0.75 mg (blue) which is the dose of the ORTHO EVRA® TDS and a lower dose 0.12mg selected to result in depletion following day 3 of application. Observed data are from BE study supporting ANDA 200910 and NDA 021180, Study NRGEEP-PHI-004/Abrams et al., 2002.

⁸⁹ Personal communication with Simcyp/Certara development team (Tariq Abdulla).

⁹⁰ Dissertation, 3.2.2.2 on page 89/164, https://refubium.fu-berlin.de/bitstream/handle/fub188/1385/Martin_Schulz_Online-Publikation_Dissertation_2009.pdf?sequence=1&isAllowed=y

⁹¹ ANDA 213950, 32p2-pharmaceutical-dev-report.pdf, EDR, accessed 06/23/2020.

The predicted PK profiles agree relatively well with the observed PK profiles although a similar PK shape with the zero-order release model discussed above was observed. This model of drug release was not deemed acceptable because it does not have the potential of evaluating the potential for drug amount depletion; assuming that diffusion through the patch remains the same when different API amounts are loaded in the patch, the predicted systemic exposure is consistent with overall different release rates as also shown on **Figure 32** above.

3. Dermal patch<Empirical release<Controlled Release: the user may input a profile of “% release over time” which indicates the % of initial amount loaded in the patch to be released following zero order kinetics by the indicated time.

The release profile is ideally the result of a manual deconvolution of the PK data to obtain an understanding of the amount of EE that is being released from the patch and reaching the systemic circulation in vivo. Due to the lack of mechanistic basis in describing drug release when utilizing this drug release model, excipient effects such as the ones by penetration enhancers may be taken into account during deconvolution and are reflected in the % drug release profile with no mechanistic basis though. Finally, potential difference in the diffusion of the API through patches of different composition and release technologies are considered during deconvolution without the consideration of a mechanism.

In the case of API depletion, assuming the same drug release profile, a lower loaded dose would result in an overall lower exposure similar to what is shown on **Figure 32**. As such this drug release model may not be ideal for predicting scenarios of drug depletion.

Regulatory history on RLD labeling and EE nominal delivery rate:

ORTHO EVRA[®] was approved under NDA 021180 on November 20, 2001 as a transdermal delivery system delivering 150/20 (NGMN/EE) µg/day per the NDA 21180 Clinical Pharmacology Review⁹². In 2006, the reference drug product labeling has been revised to omit the “rate of drug release”.⁹³ The current RLD labeling states the following under Description section:

“ORTHO EVRA is a combination transdermal contraceptive system with a contact surface area of 20 cm². It contains 6 mg NGMN and 0.75 mg EE”.

The determination of the “rate of drug release” was investigated by the Agency in 2014⁹⁴. On January 9, 2014, the Office of New Drug Quality Assessment (ONDQA) review team sent the following information request (IR) to the Sponsor:

⁹² NDA 021180, Clinical Pharmacology and Biopharmaceutics Review/Consult, Reviewer: Stephan Ortiz, date: 11/22/2005.

⁹³ DARRTS for NDA 021180: WILLIAMSON, ZETA-MAE C 05/17/2006 N/A 05/17/2006 REV-RPM-05(General Review) Supplement-20 (Labeling) Archive

⁹⁴ Division of Clinical Pharmacology 3, Office of Clinical Pharmacology, Tracking/Action Sheet for Formal/Informal Consults Reviewer: Chongwoo Yu, Ph.D. Date: 4/10/2014.

“Using your in vivo PK data from NRGEEP-CON-1016, calculate the expected delivery of EE and NGMN for currently marketed ORTHO EVRA and PIB2 formulations in units of $\mu\text{g}/24$ hours. Provide the methods, equations, values for constants, etc. utilized to calculate the estimated daily in vivo delivery rate of the product.”

The review outcomes by Yu Chongwoo are summarized below:

Systemic delivery rate from the original NDA submission dated December 21, 2000:

The calculation of systemic delivery rate from the original NDA is summarized below:

- Sponsor’s calculation of EE systemic delivery rate from ORTHO EVRA[®] was based on the study results of Study NRGEEP-PHI-014, a crossover BA study of ORTHO EVRA[®] (on either abdomen or buttock for 7 days) and 1-hour intravenous (IV) infusion of 25 μg EE + 252 μg NGMN.
- EE clearance (CL) ($\text{CL}_{\text{IV}} = \text{Dose}/\text{AUC}[0-\infty] = 30.1 \text{ L/hr}$) was calculated from single dose IV data of Study NRGEEP-PHI-014.
- CL_{IV} was multiplied by a “correction factor” of 0.6015 to obtain the corrected CL_{SS} (i.e., 18.3 L/hr).
 - Correction factor (i.e., 0.6015) was derived from a ratio of apparent oral CL for Ortho-cyclen[®] at steady state and single dose (i.e., $31.1/51.7=0.6015$).
 - Rationale for correction factor: The Sponsor believed that EE oral CL decreases with multiple dosing (based on Study NRGMON-OC-402) and should be corrected since CL_{IV} was obtained from a single dose infusion.
 - Single and multiple dose CL values of NGMN were similar; therefore, no correction was necessary for NGMN.
- Ortho Evra[®] systemic delivery rate was calculated based on: $\text{Delivery Rate} = C_{\text{SS}} \times \text{CL}_{\text{SS}}$
 - Uncorrected EE systemic delivery rate = 34.1 $\mu\text{g}/\text{day}$
 - Corrected EE systemic delivery rate = $34.1 \mu\text{g}/\text{day} \times 0.6015 = 20.5 \mu\text{g}/\text{day}$
 - It should be noted that the EE systemic delivery rate displayed above was calculated from subjects that either had Ortho Evra[®] applied to the abdomen or the buttock in Study NRGEEP-PHI-014.
- Systemic delivery rates on the label at the time of approval (i.e., November 20, 2001) = 150/20 (NGMN/EE) $\mu\text{g}/\text{day}$

Accumulation and C_{SS} : In Study NRGEEP-PHI-013, 24 healthy women were studied following with multiple doses of Ortho Evra[®] application for 3 consecutive weeks per cycle for 3 cycles.

Dr. Chatterjee’s Clinical Pharmacology review⁹⁵ concludes the following:

- No significant accumulation was observed for NGMN and EE beyond 1 week

⁹⁵ NDA 021180, Clinical pharmacology and Biopharmaceutics review, Reviewer: Dhruva J. Chatterjee, Ph.D, date: 11/16/01.

of application

- Observed PK parameters for NGMN and EE did not differ much between each of the 3 weeks of Cycle 3.

CL_{SS}: As stated above, the Sponsor concluded that following a review of more recent literature, a 40% reduction to the CL of EE, as utilized in the original analysis of the data from Study NRGEEP-P01-014 may have been overestimated or may not have been warranted (refer to the February 6, 2014 submission).

There is no direct evidence to support that a correction factor is needed to correct for the potential decrease in EE CL following multiple doses of ORTHO EVRA[®]. While acknowledging the limitations using the existing CL_{IV} data obtained from a single IV dose for 1 hour (and then extrapolating it for a 7 day wear period), it should be noted that obtaining CL_{IV} data from IV infusion for 7 days is not feasible. Given that CL_{IV} is a function of drug substance independent of its formulation, the existing data (i.e., CL_{IV}) can be used in the calculation of the systemic delivery rate of EE. the use of existing CL_{IV} (without applying a correction factor) represents a reasonable approach to calculate the systemic delivery rate of EE given the data at hand. This information will be updated as additional data are obtained from ongoing and planned studies on the systemic delivery rate of NGMN/EE from ORTHO EVRA[®].

**Clinical Review of Comparative (Threshold) Analyses
for Drug-Device Combination Products**

Division of Clinical Review (DCR)

Office of Bioequivalence (OB), Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

ANDA#	213950
Drug Product	Ethinyl Estradiol & Norelgestromin Extended Release Film
Strength(s)	0.035 mg/24HR; 0.15 mg/24HR
ANDA Applicant	Amneal Pharmaceuticals LLC
Reference Listed Drug (RLD) Name & Number	Ortho Evra® (Ethinyl Estradiol & Norelgestromin) Extended Release Film, 0.035 mg/24HR; 0.15 mg/24HR N 021180 Note: Current marketing status of RLD product is discontinued. Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons.
RLD Sponsor	Janssen Pharmaceuticals Inc.
RLD Approval Date	November 20, 2001
Reference Standard (RS) Name & No.	Xulane® (Ethinyl Estradiol & Norelgestromin) Extended Release Film, 0.035 mg/24HR; 0.15 mg/24HR ANDA 200910
RS Sponsor	Mylan Technologies Inc.
RS Approval Date	April 16, 2014
Materials Reviewed	Original Submission: 10/16/2019 Amendment: 12/18/2019 (Comparative Analysis Report), 2/18/2020 (response to FDA Information Request requesting samples)
Primary Reviewer	Zhuo J. Zhang, MD, PhD Clinical Reviewer, ANDA Team I DCR/OB/OGD
Secondary Reviewer	Michael Spagnola, MD Acting Team Leader, ANDA Team I DCR/OB/OGD
Date of Review	3/18/2020
GDUFA Goal Date	8/17/2020
DCR Comparative Analyses Conclusion	☐ No Design Differences ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

This DCR review evaluates the delivery device constituent part of the drug-device combination product intended to administer the drug product and any associated product labeling and packaging. Amneal Pharmaceuticals LLC (Applicant) submitted an abbreviated new drug application (ANDA) 213950 for Ethinyl Estradiol & Norelgestromin Extended Release Film 0.035 mg/24HR; 0.15 mg/24HR. The RLD was approved under NDA 021180. According to the Orange Book, the RLD was discontinued from market, and Federal Register notice determination is that the product was not discontinued or withdrawn for safety or efficacy reasons. ANDA 200910 (Mylan) Xulane[®] (Ethinyl Estradiol & Norelgestromin) Extended Release Film, 0.035 mg/24HR; 0.15 mg/24HR is the Reference Standard (RS) and was approved on 4/16/2014. The RLD and the proposed generic are delivered to the user via extended release film and therefore, it is considered a complex drug-device combination product.

RLD Ortho Evra[®] (Ethinyl Estradiol & Norelgestromin) Extended Release Film is indicated for the prevention of pregnancy in women who elect to use a transdermal patch. Ortho Evra[®] is intended for self-administration by patients.

This review focuses on the analysis of the user interface for the drug-device combination product (drug and a delivery device intended to administer a drug) comparing physical features and product performances between the proposed generic and the RS and comparing labeling between the proposed generic and the RLD.

1.2 Other Relevant Information

DCR has not reviewed any other comparative analyses for Ethinyl Estradiol & Norelgestromin Extended Release Film 0.035 mg/24HR; 0.15 mg/24HR according to internal databases. Another approved ANDA for Ethinyl Estradiol & Norelgestromin Extended Release Film 0.035 mg/24HR; 0.15 mg/24HR is listed in the Orange Book referencing NDA 021180 (Ortho Evra[®]).

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

2.1 Labeling comparison of the delivery device constituent part: RLD vs. Proposed Generic Product

The original product label for the RLD, Ortho Evra[®] (Ethinyl Estradiol & Norelgestromin) Extended Release Film, was approved on November 20, 2001, and the most current label was approved on 08/09/2017 (suppl-48).¹ The RLD labeling includes Prescribing Information (PI), Patient Information, and Instructions for Use (IFU).

On 12/18/2019, the applicant submitted a comparative threshold analysis report in the amendment.² The Applicant provided side-by-side labeling comparison with the most recent RLD label in their submission. Table 1 shows results of the comparison of delivery device constituent part of labeling between the proposed generic and the RLD.

¹ Drugs@FDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021180s048lbl.pdf

² <\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\contraceptive\5354-other-stud-rep\amn-xln-am-501\threshold-analysis-report.pdf>

Table 1: Labeling Comparison of the Delivery Device Constituent Part: RLD vs. Proposed

Delivery device constituent part labeling: RLD vs. Proposed	Yes/No/NA
(1) Any difference in the description/design ?	Yes, minor*
(2) Any difference in the administration or directions for use ?	No
(3) Any difference in the illustration(s)/figure(s) ?	No
(4) Any differences in the end-user IFU?	No

*Minor differences in physical features of drug-device and in picture illustration between the proposed generic product and the RLD are observed. See detail in the side-by-side labeling comparison package insert submitted on 12/18/2019 Module 1.14.3.1 [\cdsesub1\evsprod\anda213950\0002\m1\us\1-14-3-1-annotated-comparison-with-rlid.pdf](#)

Table 2: Labeling Comparison of the Instructions for Use: RLD vs. Proposed

RLD NDA 021180	Comments	Generic ANDA 213950
INSTRUCTIONS FOR USE ORTHO EVRA is for skin use only. Do not cut, damage, or alter the ORTHO EVRA patch in any way. How to start using your ORTHO EVRA patch:  Figure A		(b) (4)
• If you are not currently using hormonal birth control, you have 2 ways to begin using your ORTHO EVRA patch. Choose the way that is best for you: ○ First day start: Apply your first ORTHO EVRA patch during the first 24 hours of your menstrual period. ○ Sunday start: Apply your first ORTHO EVRA patch on the first Sunday after your menstrual period begins. Use a non-hormonal contraceptive method of birth control, such as a condom and spermicide or diaphragm and spermicide, for the first 7 days of your first cycle only. If your period starts on Sunday, apply your first ORTHO EVRA patch that day, and no back-up birth control is needed. • If you are changing from the pill or vaginal contraceptive ring to the ORTHO EVRA patch:		

<\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\contraceptive\5354-other-stud-rep\amn-xln-am-501\threshold-analysis-report.pdf>

Reviewer's Comments:

There are acceptable minor design differences between the two product pouches. The RS pouch has a notch on both edges of the pouch while the generic has an opening line on the pouch instead of the notch. The two pouches are easily opened to obtain the film (patch).

There are acceptable minor design differences in the release liner between the RS and proposed generic. The generic release liner has dimples along the four sides of the liner to prevent pressure on the film from container while the RS does not have dimples but has an extra clear film on both side of the film with similar function. Both RS and generic release liners are composed of two pieces of protective films. The method to remove the release liner is the same for two products.

There are physical differences in the width, length, area, and thickness between the proposed generic and the RS film (patch) as indicated in the table 4. For example, RS patch surface area is 14 cm² and the generic patch surface area is 12.5 cm². These are acceptable minor differences in the generic product film design.

Overall, the physical comparison supports that the proposed generic can be substituted for the RS without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

2.3 Applicant’s Comparative Task Analysis

The following table provides the comparative task analysis between the RS and the generic product. The steps to perform the task are the same between the RS and the generic.

Table 5: Comparative Task Analysis between the RS and the Proposed Generic

Task	Perception	Cognition	Action	Differences Compared with RS
Open and remove product contents from packaging	See product. See box opening. See contents.	Understand how to open the box. Know to remove the contents.	Open the box. Grasp and remove the contents or tilt the box to slide out.	No difference.
(If existing patch in place) Remove the previous patch before applying a new patch.	See the used patch.	Know to remove a used patch.	Grasp and peel the used patch from the skin.	No difference.
Choose a location to apply the patch.	None.	Know to apply at specific locations (upper outer arm, abdomen, buttock or back). Know not to place the patch where it may be rubbed by clothing or on the breasts.	None.	No difference.
Clean and dry skin.	None.	Know to clean and dry the skin.	Clean the skin.	No difference.
Open pouch and remove new patch.	See the pouch tear indicator. See separation of foil pouch. See patch.	Know to open the pouch. Know to tear the pouch along tear indicator. Know to peel pouch foil away from patch. Know to remove patch.	Grasp the pouch with one hand below the tear indicator. Grasp pouch above the tear indicator with other hand and tear. Tear open pouch.	There are minor physical differences between the pouches. The RS pouch has notches on two sides of the pouch edge to tear open the pouch. The generic has dotted lines on the top edge indicating where to tear. With the RS, there are two pieces of plastic film that sandwich the patch within the pouch. These pieces are removed with the patch but are then separated from the patch and
			Grasp and peel foil liner. Grasp and remove patch.	discarded. These are in addition to the patch liner. The generic does not have these outer pieces of plastic film. This difference is minor only. It reduces the pieces the user must handle when accessing the patch. However, the elimination of these outer plastic film pieces by the generic does not alter a critical design attribute of the patch.

Peel away ½ of liner and apply to skin.	See the liner.	Know to remove the liner. Recognize that the liner comes in two pieces. Know to apply exposed adhesive of patch to skin.	Grasp the exposed (non-overlapping) edge of one piece of the line. Grasp the patch. Pull the liner from the patch. Place adhesive side on skin.	No difference. There are minor physical differences between the patch liners (see Physical Comparison below) but the perceptual, cognitive, and action requirements for this task step and the next are the same.
Remove the other ½ of the liner and apply the entire patch to the skin.	See remaining part of the liner.	Know to remove both parts of the liner.	Grasp remaining liner. Pull the liner from the patch. Push adhesive side to skin.	No differences.
Press patch with palm and hold firmly in place		Know to press the liner fully against the skin.	Press palm against the liner.	No difference.

Source: ANDA213950 Global Submission Module 5.3.5.4. Comparative Threshold Analysis, page 18-19/24
<\\cdsesub1\evsprod\anda213950\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\contraceptive\5354-other-stud-rep\amn-xln-am-501\threshold-analysis-report.pdf>

Reviewer’s Comments:

Actual samples of the proposed generic product and the RS, Xulane®, were evaluated by this reviewer. The proposed generic product and the RS were accurately represented as described in the Applicant’s Threshold Analyses Report and other submitted documents.

The steps needed to be performed by the patient in using the medication are the same for the RS and proposed generic. This reviewer was able to open the proposed generic pouch, obtain the patch, peel away half of the clear plastic (release liner), and apply the patch appropriately. The steps needed to use the proposed generic sample provided by the Applicant match those outlined in the comparative task analysis and the instruction for use.

Overall, the comparative task analysis comparison supports that the proposed generic product can be substituted for the RS without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

3 APPLICANT’S THRESHOLD ANALYSES

On 12/18/2019, the applicant submitted a comparative threshold analysis report in the ANDA 213950 amendment. The applicant states that “No differences were found in the perceptual, cognitive, or action requirements for performance of the tasks required to prepare, apply and remove the two patches.”

Reviewer’s Comment: *DCR concludes that any differences in external design attributes are “minor” and do not affect how users perform any critical task necessary in order to use the product. The differences do not require the intervention of a health care provider and/or additional training prior to use of the proposed generic product.*

4 CONCLUSION

DCR concludes that minor design differences between the proposed generic Ethinyl Estradiol & Norelgestromin Extended Release Films, 0.035 mg/24HR; 0.15 mg/24HR, submitted under ANDA 213950 and the RS, Xulane[®] (Ethinyl Estradiol & Norelgestromin) films are acceptable.

5 RECOMMENDATION

The Clinical Discipline has completed its comparative analysis review and has no comments.



Zhuo
Zhang

Digitally signed by Zhuo Zhang
Date: 3/17/2020 10:33:53PM
GUID: 508da6fd000284836c1e087846fed896



Michael
Spagnola

Digitally signed by Michael Spagnola
Date: 3/18/2020 07:54:02AM
GUID: 56f3fc6e00e3bf2df523cd48bdc61031

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 6, 2020

TO: Bing Li, Ph.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Stanley Au, Pharm.D., BCPS
Lead Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of Global Clinical Professionals
(GCP), St.Petersburg, FL

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of a norelgestromin and ethinyl estradiol transdermal skin irritation and sensitization study (GCPAMN002) for ANDA 213950. The clinical inspection was conducted at Global Clinical Professionals (GCP), St.Petersburg, FL.

A Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, I conclude the data from the audited study is reliable.

1.1. Surveillance Recommendation

Based on the inspectional findings, studies of similar design conducted between May 2019 and the end of the current surveillance interval should be considered reliable without an inspection.

2 Inspected Studies

ANDA 213950

Study Number: GCPAMN002

Study Title: Study to Compare the Cumulative Skin Irritation and Sensitization Potential of a Generic Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 µg per day to that of Xulane Transdermal System in Normal Healthy, Adult, Human, Female Subjects Under Fasting Conditions

Dates of conduct: 05/31/2019 (first subject, first visit) -
8/1/2019 (last subject, last visit)

Clinical site: Global Clinical Professionals (GCP)
7005 4th Street N, Suite 1
St.Petersburg, FL 33702

ORA investigator Ladislav Kermet inspected Global Clinical Professionals (GCP), St.Petersburg, FL from January 14,2020 to January 17,2020.

This was the first FDA inspection of the site.

The inspection included auditing the following items:

- protocol adherence
- informed consent
- institutional review board approvals
- standard operating procedures
- test article accountability and storage
- randomization
- adverse events

3 Inspectional Findings

At the conclusion of the inspection, investigator Kermet did not issue Form FDA 483 to the clinical site. However, there were three discussion items for the inspection as described below.

a) Discussion item 1: There were certain protocol deviations that did not include specific information regarding the underlying reason to explain why the assessments were not conducted within the time window. These protocol deviations are included in the protocol deviation log from Global Clinical Professionals (Attachment 1).

A list was provided by the ORA investigator with each subject's corresponding screening and subject numbers. It is included in Attachment 2 for OGD's reference. Because it appears that the screening numbers were consistently used in presenting the GCPAMN002 clinical data, the finding does not affect the results of the GCPAMN002 transdermal skin irritation and sensitization study.

Attachments

Attachment 1-Global Clinical Professionals protocol deviation log
Attachment 2-List of corresponding GCPAMN002 screening and subject identifier numbers

Final Classification:

NAI-Global Clinical Professionals (GCP)
7005 4th Street N, Suite 1
St.Petersburg, FL 33702
FEI#: 3013959692

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Taylor/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: SA 02/04/2020, 2/5/2020
Edit: JC 2/4/2020; 2/5/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/Global Clinical
Professionals (GCP), St. Petersburg, FL, USA

OSIS File #: BE 8771

FACTS: 11970504

Stanley Au

Seongeun (Julia) Cho

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213950Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Memorandum

To: Abbreviated New Drug Applications (ANDAs) that Contain Bioequivalence Data Generated at Synchron Research Services Pvt. Ltd. (Synchron)

From: Partha Roy
Director, Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

Date: September 15, 2021

Subject: Examination of Bioequivalence Data Generated at Synchron

The purpose of this memorandum is to set forth the basis for OGD's decision to:

1. require that ANDA applicants re-conduct all bioequivalence studies for which data was generated at Synchron to confirm that the generic drug products are bioequivalent to their respective reference listed drugs (RLDs);
2. require that the re-conducted bioequivalence studies be performed at a different study site (i.e., a contract research organization (CRO) other than Synchron, or any other CRO for which the Food and Drug Administration (FDA) has publicly identified unresolved data integrity concerns); and
3. change the therapeutic equivalence rating for all approved ANDAs containing bioequivalence data generated at Synchron to "BX".

I. BACKGROUND

A. Statutory and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which established the ANDA approval process for generic drugs. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective. The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references (sections 505(j)(2)(A) and (j)(4) of the FD&C Act).

The applicant must also demonstrate that its proposed generic drug is bioequivalent to the listed drug. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the

therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.¹

A showing that the active ingredient or therapeutic ingredient in the proposed generic drug reaches the site of drug action at a rate and to an extent not significantly different from that of the listed drug, along with other information required for approval, permits FDA to conclude that the proposed generic drug can be expected to perform the same way in the body as the listed drug. Bioequivalence testing determines whether differences in formulation (e.g., differences in inactive ingredients) between a proposed generic drug and the RLD have an impact on the rate and extent to which the active ingredient becomes available at the site of action.

The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption (e.g., solid oral dosage forms) generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers. FDA has discretion to determine how the bioequivalence requirement should be met for a given product or class of products as long as its determination is not contrary to the governing statute and regulations and is based on a “reasonable and scientifically supported criterion.”² Courts have consistently upheld FDA’s implementation of the FD&C Act’s bioequivalence requirements.³

In each case, the FDA determination concerning bioequivalence is based on the reports of studies that are submitted by the applicant as part of the ANDA. FDA reviews the reports and, in the absence of evidence suggesting lack of reliability of the type that has come to light here, assumes that they accurately reflect what occurred in the studies that are the subject of those reports.

If a product is found to meet these requirements for approval under section 505(j) of the FD&C Act, it is considered therapeutically equivalent to the RLD, and is listed in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) with a code indicating therapeutic equivalence (TE). A product’s TE rating is designated by a two-letter code. The first letter of a TE code specifies whether FDA has evaluated a product as therapeutically equivalent to another product, while the second letter provides additional information regarding the basis of FDA’s evaluation.⁴ TE codes fall into two basic categories: 1) those that begin with the letter “A” (signifying that FDA considers the product to be therapeutically equivalent to another product); and 2) those that begin with the letter “B” (signifying that, at the time of the rating, actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence).⁵ A “BX” TE code is assigned to drug products for which the data that have been reviewed by FDA are insufficient to determine therapeutic equivalence; those drug products “are presumed to be therapeutically inequivalent until [FDA] has determined that there is adequate information to make a full evaluation of therapeutic equivalence.”⁶ As described in the Orange Book, “a change in a single drug product’s [TE] code from AB to BX (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment.”⁷

¹ Section 505(j)(8)(C) of the FD&C Act also provides that “[f]or a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.”

² *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992).

³ See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 (3rd Cir. 1995); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994).

⁴ Orange Book, 41st edition, at xii-xiii.

⁵ *Id.*, at xiii.

⁶ *Id.*, at xx.

⁷ *Id.*, at xxiv.

B. Factual Background

Between November 18 – 22, 2019, the Office of Study Integrity and Surveillance (OSIS) conducted a for cause inspection for two ANDAs [REDACTED] (b) (4)

[REDACTED] (b) (4) In a December 18, 2019, memorandum from OSIS to OGD/OB, OSIS stated that objectionable conditions were observed during the inspection and recommended that OGD carefully review all pharmacokinetic and subject concentration data from studies with bioanalytical portions conducted at Synchron since 2015.⁹ OGD identified anomalous data in six additional studies.¹⁰

On March 12, 2021, FDA informed Synchron of its preliminary conclusion that there is significant evidence that it has created falsified data that were submitted to FDA.¹¹ Synchron responded on April 10, 2021; however, upon review of the submitted information OGD and OSIS concluded that the information provided did not resolve the study data integrity concerns identified and that therefore data generated at Synchron cannot be relied upon to support the approval of any applications submitted to FDA.¹²

Specifically, OSIS and OSI determined that Synchron's April 10, 2021 response failed to explain the numerous instances of overlapping subject sample concentration-time profiles and anomalous pharmacokinetic (PK) trends that deviated from the normal population distribution, which raises significant concerns for the bioanalytical and bioequivalence test results generated at Synchron that are submitted to FDA in support of ANDAs. OSIS and OSI concluded that the manner in which Synchron conducted the studies described in the March 12, 2021 letter causes FDA to believe that the reliability and validity of study data generated by Synchron cannot be assured.¹³ Because Synchron has been responsible for the creation of false data in those studies, FDA has no reason to believe that any data that Synchron has produced is reliable. Thus, FDA has determined that all study data from all studies conducted at Synchron must be rejected.

II. DISCUSSION

Whether or not a generic drug is bioequivalent to the innovator it copies determines whether or not that generic drug is safe and effective to be used by patients. The statutory scheme for approval of drugs is highly dependent on the probity of those who conduct the studies upon which FDA decisions are based, including bioequivalence studies. FDA does not itself perform these studies. Instead, it reviews the reports of studies

[REDACTED] (b) (4)

⁹ See Memorandum to B. Li (OB) fr. K. Scheibner and M. Cobourne-Duval (OSIS) re "For Cause inspection of Synchron Research Services Pvt. Ltd., Ahmedabad, Gujarat, India" (Dec. 18, 2019), available at <https://panorama.fda.gov/document/view?ID=5dfb6f43003521adf6472c53a6310b0a>.

¹⁰ OB's evaluation of the data submitted in these six additional studies is available here:

ANDA 209720: <https://panorama.fda.gov/program/view?ID=5864a96100f5962f3f9f682d0d919aab>;

ANDA 210831: <https://panorama.fda.gov/program/view?ID=59d45d91003666b93deced859814b713>;

[REDACTED] (b) (4)

See Letter to S. Rathnam (Synchron) fr. S. Kassim (OSIS) (Mar. 12, 2021).

¹² OSIS Review of Synchron Response.

¹³ See Letter to S. Rathnam (Synchron) fr. S. Kassim (OSIS) and D. Burrow (OSI) (Sept. 15, 2021).

provided by applicants. FDA has a limited ability to inspect testing facilities that submit such reports, and cannot do intensive inspections with respect to every study submitted.

When the evidence available to FDA demonstrates that a facility has intentionally produced falsified data that are submitted to FDA, and there is no evidence that the falsification is limited to particular studies, FDA is justified—indeed compelled—to assume that any data that that facility has submitted is unreliable. Thus, FDA lacks data on which it can rely to determine that the drug covered by this ANDA is safe and effective or that it is therapeutically equivalent to the innovator that it copies.

Based on the data anomalies identified by OGD and OSIS, the subsequent review of Synchron’s April 10, 2021 response, and OSIS’s and OSI’s conclusion that all study data from all studies conducted at Synchron must be rejected, OGD has determined that the bioequivalence data generated at Synchron is unreliable.¹⁴ Therefore, the information submitted to FDA to support ANDAs based on studies conducted at Synchron is insufficient to show that a generic drug product is bioequivalent to its RLD, and an ANDA cannot be approved, in accordance with section 505(j)(4)(F) of the FD&C Act.

This determination is applicable to all bioequivalence data generated at Synchron, including both the clinical and bioanalytical sites. While the initial focus of OSIS and OB’s investigation was the bioanalytical site, the data anomalies observed at the bioanalytical site could be the result of misconduct at either the clinical or bioanalytical sites.¹⁵ Moreover, lack of data integrity in analysis suggests the potential for lack of integrity in the work of the clinical sites. These sites share the same senior management and are located in close proximity, in the same city and state. Synchron’s April 10, 2021 response categorically denied any data error and falsification and did not propose any corrective or preventative actions to address the identified data anomalies, which raises serious concerns regarding the overall quality management system. It is therefore not possible to conclude that the data generated at Synchron’s clinical site is reliable either. This reflects the final determination of OGD/OB, and supersedes any prior statements or reviews of this data.

In addition, for any approved ANDAs that contained bioequivalence data generated at Synchron, the TE code should be changed to “BX”, as applicable,¹⁶ until additional data establishing the bioequivalence of the drug products to their respective RLDs is submitted. Based on the severity of the data integrity concerns documented

¹⁴ OSIS and OSI recommend rejecting study data from all studies conducted at Synchron. Based on the earliest identified ANDA submission, OGD believes the earliest bioequivalence studies conducted at Synchron that could have been submitted to FDA occurred in December 2007 (for the clinical site) and (b) (4). However, due to the limitations of and changes to record keeping methods, OGD faces challenges in identifying all ANDAs submitted to the FDA that contain data generated at Synchron. Prior to October 1, 2014, the date that OGD began managing ANDA reviews within the Center for Drug Evaluation and Research’s integrated electronic informatics review platform (Panorama), FDA’s information management systems, such as COMIS and CDER Division File System (DFS), lacked the capability to integrate site-specific information for studies submitted in ANDAs. This information was sporadically recorded in internal databases, including OB’s Review File System (RFS) and shared drive (V drive) which are no longer in use, or was retrieved manually by searching individual ANDA paper jackets or electronic submissions. Manual review is particularly challenging during the COVID-19 public health emergency, as it requires the retrieval, shipment, and physical review of documents. In light of these considerations, OGD has determined that that it is reasonable to take the actions described in this memorandum although the list of impacted ANDAs we have identified may exclude some ANDAs that cannot be found through available electronic search tools, primarily Mercado Search 360. This determination is based on the following factors: 1) the risk to FDA staff and contractors to conduct such a manual review during a pandemic; 2) the public health impact of delaying a rejection of unreliable data in already identified ANDAs while the manual review occurs; and 3) the likelihood that such a manual review will nonetheless fail to identify all impacted ANDAs.

¹⁵ For example, switching or mislabeling of subject samples at the clinical site could produce the data anomalies observed; however, the root cause of the specific data anomalies observed remains unknown.

¹⁶ Over-the-counter (OTC) drug products and drug products in the Discontinued Drug Product List do not have TE codes assigned in the Orange Book.

at Synchron, OGD has determined that it cannot rely on any bioequivalence data generated at Synchron to make a full evaluation of therapeutic equivalence of an ANDA that contained such data. OGD will give applicants the opportunity to re-conduct any affected bioequivalence studies; however, if an applicant does not re-conduct the studies at a different site within a reasonable amount of time, OGD will consider whether to initiate proceedings to withdraw approval of the ANDA, pursuant to section 505(e) of the FD&C Act and 21 CFR 314.150.

III. CONCLUSION

Based on the information discussed and referenced above, OGD will:

1. require that ANDA applicants re-conduct all bioequivalence studies for which data was generated at Synchron to confirm that the generic drug products are bioequivalent to their respective RLDs;
2. require that the re-conducted bioequivalence studies be performed at a different study site (i.e., a CRO other than Synchron, or any other CRO for which FDA has existing unresolved publicly identified data integrity concerns); and
3. change the therapeutic equivalence rating for all approved ANDAs containing bioequivalence data generated at Synchron to “BX”.

This determination supersedes any prior bioequivalence assessments by OGD/OB for the affected ANDAs, and the bioequivalence review status for the affected ANDAs is considered to be inadequate-major.

(b) (4)

V. APPENDIX 2: Deficiency language options for affected ANDAs**For all ANDA letters:**

Your ANDA contains bioequivalence data generated at Synchron. The Food and Drug Administration (FDA or the Agency) recently concluded that Synchron did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of bioequivalence studies. The manner in which Synchron conducted multiple studies causes FDA to believe that the reliability and validity of study data generated by Synchron cannot be assured. As a result, FDA has significant concerns about the validity and reliability of bioequivalence and bioavailability data generated at Synchron that was submitted to the FDA in support of ANDAs and new drug applications. FDA issued an “Untitled Letter” to Synchron on September 15, 2021 that reflects these conclusions and provides additional detail, see: [fda.gov/media/151570/download](https://www.fda.gov/media/151570/download).

The Office of Generic Drugs (OGD) concludes that the integrity and accuracy of data generated at Synchron, including the data generated by Synchron that you submitted in this application, cannot be assured. Therefore, OGD will not accept data generated at Synchron as a basis to approve your application. You must therefore re-conduct those bioequivalence studies (b) (4) (b) (4) at an alternate contract research organization (CRO) (i.e., a CRO other than Synchron, or any other CRO for which FDA has publicly identified unresolved data integrity concerns).

For approved, Rx ANDA letters only, add the following:

In addition, OGD is today changing the therapeutic equivalence (TE) evaluation code for your product in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) to “BX.” A “BX” code is assigned to drug products for which the data that have been reviewed are insufficient to determine therapeutic equivalence; “the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.”¹ Due to the concerns about data generated at Synchron described above, OGD has determined that new bioequivalence studies (both bioanalytical and clinical portions) at an alternate CRO are necessary to provide adequate information to make a full evaluation of the therapeutic equivalence of your drug product to its reference listed drug.

Please respond to this letter within 30 days with a general correspondence to your application. The general correspondence should either describe your plans to re-conduct these studies in order to submit your supplement within the next year, including the specific study numbers to be re-conducted, or request withdrawal of your application. If the general correspondence is not received within 30 days, FDA may initiate proceedings to withdraw the approval of your ANDA.

If you have any questions, call Ted Sherwood, Director, Office of Regulatory Operations, at (301) 796-1605.

For tentatively approved ANDA letters only, add the following:

Please respond to this letter within 30 days with a general correspondence to your application. The general correspondence should either describe your plans to re-conduct these studies in order to submit your amendment within the next year, including the specific study numbers to be re-conducted, or request withdrawal of your application. If the amendment is not received within 30 days, FDA will issue a complete response letter, placing your application in a “complete response” status, which means it will no longer be tentatively approved.



ANDA 213950

POST-CRL MEETING REQUEST DENIED

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on August 18, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day.

We also refer to your correspondence received on August 18, 2020, requesting a post-complete response letter meeting to clarify deficiencies noted in the complete response letter issued by this office on August 14, 2020.

Your request for a post-complete response letter meeting is denied because the purpose of a post CR meeting is to clarify the deficiency comments in the CR letter. In your post CR meeting request, you provided rationale to address the deficiency in the CR letter that the difference in the proportion of subjects who have concentrations of Ethinyl Estradiol below 25 pg/mL at 168 hours is not expected to lead to differences in safety or efficacy between the Test and Reference Products. You asked whether the Agency agrees that the range of observed concentrations is a better indicator of efficacy and safety between the Test and reference Products rather than the proportion of subjects below the threshold value of 25 pg/mL at 168 hours. However, these are not clarification questions with respect to the CR letter. Therefore, your post CR meeting request is denied. You may amend your current application to include your justifications in a Post CR amendment. The Agency will evaluate the information for this application, at that time..

If you have any questions, please contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe

Date: 8/26/2020 07:06:20PM

GUID: 54205223000198472e8a989db47b1636

POST COMPLETE RESPONSE MEETING REQUEST DENIAL - BIOEQUIVALENCE

ANDA No.	213950
Drug Product	Norelgestromin and Ethinyl Estradiol Transdermal System
Strength(s)	150 µg /35 µg/day
Applicant Name	Amneal Pharmaceuticals LLC
Post CR Meeting Request Date	August 18, 2020
Primary Reviewer	Madhusudana Rao Chaluvadi, Ph.D.
Secondary Reviewer	Li Xia, Ph.D.
Tertiary Reviewer	Ke Ren, Ph.D.
Firm's Reconsideration Request	Requesting a post complete response meeting

The Division of Bioequivalence III (DBIII) has completed the review of your request for the Post Complete Response (CR) meeting to discuss the deficiency comments noted in the CR letter dated August 17, 2020, and has the following response:

The purpose of a post CR meeting is to clarify the deficiency comments in the CR letter. In your post CR meeting request, you provided rationale to address the deficiency in the CR letter that the difference in the proportion of subjects who have concentrations of Ethinyl Estradiol below 25 pg/mL at 168 hours is not expected to lead to differences in safety or efficacy between the Test and Reference Products. You asked whether the Agency agrees that the range of observed concentrations is a better indicator of efficacy and safety between the Test and reference Products rather than the proportion of subjects below the threshold value of 25 pg/mL at 168 hours.

However, these are not clarification questions with respect to the CR letter. Therefore, your post CR meeting request is denied. You may amend your current application to include your justifications in a Post CR amendment. The Agency will evaluate the information for this application, at that time.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MEETING NOTES: Office of Bioequivalence, Division III

Internal Meeting Minutes

Date: August 4, 2020
Time: 4:00 PM – 5:00 PM
Meeting Location: WebEx

Drug Product: ANDA 213950: Norelgestromin and Ethinyl Estradiol Transdermal System (TDS), 150 µg /35µg/day

RLD: Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day (NDA 021180, discontinued)

RS: Xulane® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day (ANDA 200910)

Meeting Attendees:

Office of Generic Drug/Immediate Office (OGD/IO):
William (Bill) Chong, M.D., Associate Director for Clinical Affairs

Division of Clinical Review (DCR)
Kachikwu Illoh M.D., Director
Lolita Lopez, M.D., Acting Deputy Director

Michael Spagnola M.D., Acting Team Leader
Zhuo (Joe) J. Zhang, M.D., Ph.D., Primary Assessor

Division of Bioequivalence III (DBIII)
April Braddy, Ph.D., RAC, Acting Director
Ke Ren, Ph.D., Acting Deputy Director
Wendy Cai, Ph.D., Acting Associate Director
Li Xia, Ph.D., Team Leader
Madhusudana Chaluvadi, Ph.D., Primary Assessor
Issa Nesheiwat, Pharm.D, Project Manager (*Meeting Recorder*)

Objective:

This is a follow-up meeting to discuss with DCR if there are any concerns on the lower ethinyl estradiol (EE) concentration of test product at 168 hrs (patch removal) in Amneal's PK study from clinical perspective.

Background:

- Amneal submitted a single-dose, two-way crossover study comparing its test product, Norelgestromin and Ethinyl estradiol, 150 µg /35 µg/day to the reference

MEETING NOTES: Office of Bioequivalence, Division III

standard (RS), Mylan's Xulane® (ANDA 200910), with both patches applied at abdominal site.

- On 07/30/2020, DBIII met with the Office of Bioequivalence/Immediate Office (OB/IO), DCR and division directors in Division of Bioequivalence (DB) to discuss two issues of Amneal's test products: 1) whether sufficient loading EE dose in test product when applied to the non- abdominal site; and 2) any concerns on lower than <25 pg/mL of EE concentration at 168 hrs observed in some individual subjects with test treatment from clinical perspective. Innovator of Ortho Evra identified C_{ss} target ranges of 25-75 pg/mL of EE for optimum efficacy.¹ However, the meeting was inconclusive due to the time limitation.
- This is a follow up meeting with DCR to seek their expert opinion on the clinical concerns for higher % of individual subjects' concentrations lower than 25 pg/ml in the test treatment Please refer to attached slides for the details.

Discussion:

- From the concentration time profiles of individual subjects in Amneal's PK study at the abdominal site (slide#4), the team pointed out that there are few subjects from both test and RS treatments who never reached EE concentrations that exceeded the lower therapeutic range of EE concentration of 25 pg/ml during the whole wear period.
- The team also explained that the mean concentration for the test product (i.e., 29.5 pg/ml) at 168 hours is within the C_{ss} target range of 25-75 pg/ml of EE though the data show that the EE concentrations for 38.9% (28 subjects) of the total subjects at 168 hours were lower than 25 pg/ml for the test product, compared to 16.7% (12 subjects) of the total subjects for the reference product. The team also presented that based on multiple dose simulation using superimposable approach, the 90% CI of C_{min} failed to meet BE criteria and added that in the current product specific guidance (PSG), the BE determination is based on C_{max} and AUCs where pAUC and C_{min} are not recommended. For this reason, DBIII requested DCR's input if there is any clinical concern and also if efficacy of TDS is associated with AUC or concentration for EE.
- Joe stated that EE concentrations are critical for safety and efficacy. There appears to be a potential difference in EE concentrations between test and reference, and that concentrations below 25 pg/mL may be subtherapeutic. The DB team pointed out that pAUC₀₋₁₆₈ and pAUC₇₂₋₁₆₈ met the BE criteria. The upper bound of 90% CI for pAUC₀₋₇₂ slightly exceeded 125.00%.
- DCR noted that the significant differences of EE concentration between test and reference products at 168 hrs (patch removal) does raise questions and concerns. It

¹ DARRTS, NDA 021180, CHATTERJEE, DHRUBA J, 11/19/2001, REVCLINPHARM-01(General Review)

MEETING NOTES: Office of Bioequivalence, Division III

was noted that there are significant higher number of subjects with EE concentrations less than 25 pg/ml and between 20-25 pg/ml for the test product compared to reference. Only 61.1% subjects (44 subjects) reached target therapeutic concentrations (> 25 pg/ml of EE) for test product compared to 83.3% subjects (60 subjects) for RS product. This may be meaningful but DCR does not have enough information to draw conclusions with certainty. DCR was not clear on the degree of certainty there was for use of a lower concentration threshold of 25 pg/mL and could not opine on how critical the concentration on a single day was for ensuring adequate exposure to yield efficacy equivalent to the RLD.

- Bill asked how the AUC or concentration levels look like for the other component, NGMN. DBIII mentioned that concentration vs. time profiles for the test and RS product are overlapped and T/R ratio of AUCs and Cmax is around 1. DBIII volunteered to send the details of NGMN PK profile after the meeting.
- Based on the discussion during the meeting, DBIII management (April) proposed to send a deficiency asking the applicant to address the concerns and to send a formal consult to DCR after receiving the applicant's responses. DCR management agreed with DBIII's proposal.

Action Items:

- DBIII will draft a deficiency letter to ask Amneal to address our concerns on the significant higher number of subjects with lower than 25 pg/ml EE concentrations at 168 hours for the test product (28 subjects) compared to the reference product (12 subjects). DCR agreed to provide comment on the deficiency letter. DBIII will incorporate the deficiency letter after DCR gives their input/feedback.
- DBIII will send a formal consult to DCR on this issue once Amneal provides response.

Final Action/Outcome:

- DBIII drafted a deficiency and sent it through e-mail to DCR on 08/07/2020 and the deficiency letter was agreed upon between DBIII and DCR on 8/11/2020.

Attachment:



ANDA 213950 D
M ti 0804202

MEETING NOTES: Office of Bioequivalence, Division III

Drafted by Issa Nesheiwat, 08/10/2020

Revised by Madhusudana Chaluvadi, 08/11/2020 and 08/13/2020

Revised by Li Xia, 8/11/2020 and 8/13/2020(2)

Revised by Ke Ren, 8/11/2020 and 8/13/2020(2)

Reviewed by Wendy Cai, 8/11/2020 and 8/13/2020

Reviewed by April Braddy, 8/13/2020 (2) and 08/14/2020

MEETING NOTES: Office of Bioequivalence, Division III

Internal Meeting Minutes

Date: July 30, 2020
Time: 4:00 PM – 5:00 PM
Meeting Location: Webex

Drug Product: ANDA 213950:
Norelgestromin and Ethinyl Estradiol Transdermal System (TDS), 150 µg /35µg/day

RLD: Ortho Evra® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day (NDA 021180, discontinued)

RS: Xulane® (norelgestromin and ethinyl estradiol) Transdermal Film, Extended Release, 150 µg /35 µg/day (ANDA 200910)

Meeting Attendees:

Office of Bioequivalence/Immediate Office (OB/IO):
Nilufer Tampal, Ph.D., Acting Deputy Director

Office of Bioequivalence (OB)

Division of Bioequivalence III

April Braddy, Ph.D., RAC, Acting Director, DBIII
Ke Ren, Ph.D., Acting Deputy Director, DBIII
Wendy Cai, Ph.D., Acting Associate Director, DBIII
Li Xia, Ph.D., Team Leader, DBIII
Madhusudana Rao Chaluvadi, Ph.D., Primary Assessor, DBIII
Issa Nesheiwat, Pharm.D., Project Manager, DBIII

Division of Bioequivalence II

Hongling Zhang, Ph.D., Acting Director, DBII

Division of Bioequivalence I

Utpal Munshi, Ph.D., Acting Director, DBI
Rong Wang, Ph.D., Acting Associate Director, DBI

Division of Clinical Review

William Chong, M.D., Acting Director
Lolita Lopez, M.D., Acting Deputy Director
Carol Kim, Pharm.D, Acting Associate Director
Micheal Spagnola M.D., Acting Team Leader
Zhuo J. Zhang, M.D., Ph.D., Primary Assessor

MEETING NOTES: Office of Bioequivalence, Division III

Objectives:

- (1) To discuss DBIII's responses to address OPQ's concern on low ethinyl estradiol loading dose issue for ANDA 213950, Norelgestromin (NGMN) and Ethinyl Estradiol (EE) Transdermal System, 150/35 mcg/day and decide if an additional BE study at a non-abdomen site is needed to demonstrate BE; and (2) To discuss whether there are any concerns on the lower EE concentrations for the test product at 168 hrs (at the time of patch removal) in Amneal's PK study.

Background:

- Amneal submitted an in vivo PK endpoint study on Norelgestromin and Ethinyl estradiol, 150 µg /35 µg/day. Both test and RS patches were applied at abdominal site. The test formulation contains 0.289 mg loading dose, which is only 54.5% of the EE loading dose in the RS, Xulane® (0.53 mg) and 38.5% of EE loaded in the RLD, Ortho Evra® (0.75 mg). For the BE study in ANDA 200910 (RS, Xulane) comparing to the RLD, the patches were applied to upper back side of the body with an overlay.
- Based on previous discussion with OPQ,¹ it was assumed that if Mylan's (RS, ANDA 200910) EE delivery rate derived from residual drug analysis data at a non-abdomen site is an accurate measure of EE delivery (~53 µg/day for RS and ~66 µg/day for RLD), Amneal's test product would essentially be fully depleted of EE (289 µg) by ~ Day 5.5 of the 7-day wear period at non-abdominal site. For this reason, OPQ raised a question whether an additional BE study is warranted at non-abdomen site to demonstrate BE of current test product.
- Based on the mean concentration vs. time profiles, there is a rapidly decrease of EE concentration in Amneal's test product (compared to the reference product, Xulane®) after 72 hrs and until 168 hours. This raised a potential concern that the slower release observed in the test product may be due to the low loading dose of EE which might result in insufficient excess of drug available within the TDS after 72 hours. The applicant was asked to address this concern in the DRL letter issued on 5/12/2020.
- On 05/16/2020, DBIII sent a consult request to the Division of Quantitative Methods and Modeling (DQMM) regarding employing modeling and simulation methodologies to address concerns on potential insufficient EE loading dose for the test product. In DQMM's consult response, it concluded that an additional BE study on non-abdomen site is not needed as the Test and the RS products are expected to be following patch application on the back and no EE depletion is expected when the Test product is applied on the back under labeled conditions (no overlay).

¹ <https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>, Document: A213950N000DB-MeetingMinutes01-04082020.docx

MEETING NOTES: Office of Bioequivalence, Division III

- Based on the review team's calculation, pAUC₀₋₁₆₈ and pAUC₇₂₋₁₆₈ met BE criteria. Using superimpose simulation approach at 3rd patch application, the results indicate that the AUC_{tau} and C_{max} are within the BE limits, but the lower limit of 90% CI for C_{min} is slightly less than 80%.

Discussions:

- DBIII initiated the discussion whether an additional BE study on non-abdominal site was necessary. The team shared that overlay was used in Mylan's application. Therefore, the delivery rate of EE calculated from residual drug analysis maybe be overestimated. Based on residual analysis from Amneal's PK study at abdomen site and DQMM simulation results, DBIII deemed that an additional BE study at non-abdominal site is not necessary. DBIII asked if an agreement could be reached. However, there was no agreement reached due to clinical concerns raised by DCR and need for further discussion.
- Discussion was then transitioned to focus on the lower EE concentrations (<25 pg/mL) at 168 hrs patch removal for some individual subjects. The team shared the point that the mean concentration for the test product (i.e., 29.5 pg/ml) at 168 hours is within the target range (25-75 pg/mL). However, DCR brought up the concerns on the significant number of subjects with test treatment having low EE concentrations at end of wearing period of 168 hour (patch removal) as 28 subjects of the 72 subjects had concentrations lower than 25 pg/mL, compared to 12 subjects from the reference product. In addition, based on individual concentration vs time profile for Amneal's PK study, the team pointed out that EE concentrations for few subjects with both test and RS treatments never reach the therapeutic window of 25 pg/mL during the whole wearing period.
- DBIII shared that the lower EE loading dose in Amneal's patch which was previously raised by OPQ, although they did not include these concerns in their deficiency letter.
- Most of the scientific discussion within the meeting was focused on the clinical concerns being raised by DCR as it relates to the individual concentrations of EE varying significantly at 168 hours (patch removal) between the test and reference product and being outside the therapeutic window.
- Also, OB IO and DBs asked the below clarifying questions which were unable to be addressed fully during the meeting based on the extensive discussion to the above point. The following additional questions were raised during the meeting:
 1. Mylan and Teva's BE studies were conducted in Caucasians and African Americans and Amneal's study was conducted in Indian population (Asian), is there an impact of study population on the PK of EE according to the RLD labeling?

MEETING NOTES: Office of Bioequivalence, Division III

2. Is there any association between patch adhesion score and the lower concentrations observed for test product at 168 hrs?
3. Is the efficacy associated with AUC or concentration of EE, especially the concentration at steady state ?
4. How important is the therapeutic window of 25-75 pg/ml EE?
5. How important is the Cmin for therapeutic efficacy?
6. Why don't we have a concern on the loading dose for NGMN?

Action Items:

1. DBIII will schedule a follow-up meeting with DCR to further discuss the clinical concern on the lower EE concentration of test product at 168 hrs (patch removal) in Amneal's PK study.
2. DBIII will follow-up with OB IO and DBs on the questions posed during the meeting and any other additional questions based on the information presented in the meeting.

Final Action/Outcome:

DBIII scheduled the following up meeting with DCR which was held on 08/04/2020,² and DBIII submitted responses to the questions posed by email on 08/10/2020 (see attachment #2).

Attachments:

1) DBIII presentation to OB/IO 07/30/2020



ANDA 213950 OBIO
Meeting 07302020.p

2) DBIII responses to the post-meeting questions³

² GDRP: A213950N000DB-MeetingMinutes01-08042020.docx at

<https://panorama.fda.gov/task/view?ID=5dfb984600023e07a0599fc7df9d912c>

³ [\\fda.gov\wodc\CDER\OGD\All\OGDS11\DIVISION\BIO\BIO3\Email Communications\ANDA 213950 Norelgestromin and Ethinyl Estradiol Transdermal System](https://fda.gov/wodc/CDER/OGD/All/OGDS11/DIVISION/BIO/BIO3/Email%20Communications/ANDA%20213950%20Norelgestromin%20and%20Ethinyl%20Estradiol%20Transdermal%20System)

MEETING NOTES: Office of Bioequivalence, Division III



RE_ ANDA 213950
Norelgestromin and

Drafted by Issa Nesheiwat, 8/11/2020

Reviewed by Madhusudana Chaluvadi, 8/11/2020, 8/13/2020 and 8/17/2020

Reviewed by Li Xia, 8/11/2020, 8/13/2020 and 8/17/2020

Reviewed by Ke Ren, 8/11/2020, 8/13/2020 (2) and 8/17/2020

Reviewed by Wendy Cai, 8/11/2020 and 8/13/2020

Reviewed by April Braddy, 8/13/2020 (2), 8/14/2020, 08/17/2020

ANDA 213950

DISCIPLINE REVIEW LETTER
No Comments

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719

Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Ms. Edwards:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 18, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Norelgestromin and Ethinyl Estradiol Transdermal System, 150/35 mcg per day.

The Division of Labeling has no further questions/comments at this time based on your labeling submission received December 18, 2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

Please note that we are providing this preliminary determination to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, this preliminary determination does not reflect a complete review of your application and should not be construed as such. In addition, this determination does not necessarily reflect input from supervisory levels. You should be aware that this determination may be modified as we complete our review.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at:

<https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

U.S. Food & Drug Administration

10903 New Hampshire Avenue

Silver Spring, MD 20993

www.fda.gov

in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Julie
Call

Digitally signed by Julie Call

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ANDA 213950

INFORMATION REQUEST

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road
Brookhaven, NY 11719
Attention: Candis Edwards
Senior Vice President, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 18, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Norelgestromin and Ethinyl Estradiol Patch, 35 mcg/24 hr and 150 mcg/24 hr.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Biopharmaceutics

1. Provide data (with appropriate statistics) to support the discriminating ability of your proposed *in-vitro* drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the drug release profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters ((b) (4) (b) (4) In addition, if available, submit data showing that the selected method is able to reject batches that are not bioequivalent to the reference batch.
2. Provide the complete drug release profile data [individual (n=12), mean, range, % CV at each time point, and mean profiles] in QC medium for batches PW-ST-18021B and PW-ST-18022B for your proposed drug product in a tabulated form. Also provide the details on manufacturing date, site, size and the drug release test date.

We request a prompt written response, no later than April 6, 2020, in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date

assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Steven Yang, Regulatory Business Process Manager, at steven.yang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Steven Yang
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Steven
Yang

Digitally signed by Steven Yang

Date: 3/06/2020 06:25:21PM

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 10, 2019

FROM: Martin Shimer
Deputy Director, Division of Legal and Regulatory Support
Office of Generic Drug Policy

TO: Abbreviated New Drug Application (ANDA) for Combined Estrogen-Progestogen Contraceptives (COCs) or Progestogen-only Contraceptives (POCs).

SUBJECT: Pending Citizen Petition for Hormonal Contraceptives (FDA-2019-P-2289)

The purpose of this memorandum is to document the Office of Generic Drug's (OGD's) awareness of a pending citizen petition for hormonal contraceptives—COCs and POCs, including medroxyprogesterone acetate injection.

Background

A citizen petition (FDA-2019-P-2289) from the Contraceptive Study Group was received by the Food and Drug Administration (FDA or the Agency) on May 10, 2019. The petition requests that the Agency remove depot medroxyprogesterone acetate (DMPA; Depo Provera) from the market. The petition also requests the Agency add black box warnings to the prescribing information and add safety information to the labeling or patient-related materials for COCs and POCs for various diseases, ailments, or conditions. On June 26, 2019, the petitioners revised the petition by adding additional studies and information about new and previously referenced studies.

Specifically, the petition requests, for both COCs and POCs that the Agency require:

- 1) A black box warning regarding alleged risk of breast cancer and that patient-related materials adequately convey such risk.
- 2) A black box warning regarding alleged risk of cervical cancer and that patient-related materials adequately convey such risk.
- 3) An amendment to black box warnings regarding cigarette smoking and serious cardiovascular events on some formulations and addition of a black box warning on all hormonal birth control products regarding the alleged risk of venous thrombosis and cardiovascular disease; that patient-related materials clearly explain such risks; and direct-to-consumer advertising include warnings of such risk.
- 4) A warning on the labeling regarding alleged risk of bone fractures and that patient-related materials adequately convey such risks.

In addition to those mentioned above, the petition also requests FDA to require the following for COCs:

- 1) A black box warning regarding alleged risk of inflammatory bowel disease and that patient-related materials adequately convey such risk.
- 2) A black box warning regarding alleged risk of systemic lupus erythematosus (SLE) and that patient-related materials adequately convey such risk.
- 3) A black box warning regarding alleged risk of depression and suicide and that patient-related materials adequately convey such risks.
- 4) A warning on the labeling regarding alleged risk of multiple sclerosis (MS) and that patient-related materials adequately convey such risks.
- 5) A warning on the labeling or prescribing information regarding various alleged urogenital problems and that patient-related materials adequately convey alleged risk of interstitial cystitis.

In addition to those previously mentioned, the petition also requests FDA to require the following for POCs:

- 1) An addition to the labeling, patient-related materials, and direct-to-consumer advertising regarding alleged risk of increase in fat body mass.

FDA is still considering the issues raised in the citizen petition.

DISCUSSION

Prior to taking an action on this ANDA, FDA considered whether the application implicated any of the issues raised in the pending citizen petition submitted by the Contraceptive Study Group. Upon review of the petition and this ANDA, FDA has determined, as detailed below, that the issues raised in the citizen petition are not implicated by the ANDA, and thus need not be resolved by the agency prior to taking an action on the ANDA.

Regarding the request to withdrawal Depo-Provera from the market, the issues raised in the citizen petition do not provide a basis for why FDA may not approve this ANDA or any supplement unless or until FDA takes action with respect to the RLD. An applicant seeking approval of a proposed generic drug under an ANDA submitted under section 505(j) of the Federal Food, Drug, and Cosmetic (FD&C) Act is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the ANDA applicant relies on FDA's finding that a previously approved drug product, i.e., the reference listed drug (RLD), is safe and effective, and must demonstrate, among other things, that the proposed generic drug is the "same" as the RLD and is bioequivalent. Specifically, with limited exceptions, a drug product for which an ANDA is submitted must have, among other things, the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.¹ Therefore, FDA's refusal to approve an ANDA for safety and efficacy reasons generally must be preceded by the RLD's withdrawal or suspension, or proposal to withdraw the RLD, for safety and efficacy reasons² and withdrawal for reasons of safety and efficacy of generic drug products using Depo-Provera as their RLD

¹ Sections 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

² 21 CFR 314.127(a)(9)-(11).

generally would be preceded by a determination that Depo-Provera itself is not safe and/or effective.³

Pursuant to the FD&C Act, a drug product described in an ANDA must contain the same labeling as the RLD (with certain permissible differences).⁴ At this time, ANDAs will be compared to that of the approved RLD, consistent with the statute and regulations. Depending on resolution of the issues raised in the petition, OGD will take any appropriate action with respect to this ANDA, such as requiring the ANDA to update its labeling to match the RLD labeling if FDA's review of the issues raised in the petition results in changes to the RLD labeling.⁵

CONCLUSION

Based on the foregoing, OGD has determined that the citizen petition does not prevent OGD from taking action on this ANDA before resolution of the petition. Depending on resolution of issues raised by the petition, OGD will take action as appropriate, with respect to this ANDA.

³ 21 CFR 314.151(a).

⁴ Sections 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

⁵ To the extent the citizen petition requests actions related to labeling that FDA does not approve as part of the ANDA review process (e.g., promotional labeling) and advertising materials, we note that these requests are not germane to the question of whether this ANDA can be approved. We note that any such materials utilized by an ANDA applicant would need to be reported to FDA under 21 CFR 314.98(b) and 314.81(b)(3)(i) and would be subject to applicable statutory and regulatory requirements.

ANDA 213950

INFORMATION REQUEST

Amneal Pharmaceuticals LLC
50 Horseblock Road
Brookhaven, NY 11719

Attention: Candis Edwards
candis.edwardsRA@amneal.com

Dear Candis Edwards:

This is in reference to your abbreviated new drug application (ANDA), received on December 18, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Norelgestromin and Ethinyl Estradiol Transdermal System, 150 mg/35 mcg per day.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

We request at least 2 samples of the proposed product for each strength, and at least 2 samples of each strength of the RLD. The proposed product should be affixed with the to-be-marketed immediate container label, or a label that closely resembles the to-be-marketed product. For the proposed product, samples with a mocked label, i.e., non-commercially produced, depicting the actual label in both size, shape and font would be acceptable. Placebo samples are acceptable.

Refrigeration is not needed for samples.

The requested samples should be submitted under a separate cover letter and mailed to the following address:

Teena Thomas Pharm.D.
Senior Regulatory Project Manager
Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Bldg. 75, Room 2628
10903 New Hampshire Ave,
Silver Spring, MD 20993

We request the samples no later than February 19, 2020 in order to continue our evaluation of your ANDA.

INFORMATION REQUEST CLINICAL

If you do not submit the requested information(samples) by February 19, 2020, the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Teena.Thomas@fda.hhs.gov

Please also confirm receipt of this letter.

Sincerely,

Teena Thomas, Pharm.D.
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Teena
Thomas

Digitally signed by Teena Thomas

Date: 2/05/2020 01:56:49PM

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