A Randomized, Double-blind, 2-Way Crossover Bioequivalence and Adhesion Study of a Transdermal Contraceptive Patch Manufactured with Newly Sourced Adhesive Components at the End of Shelf Life and Currently Marketed EVRA® at the Beginning of Shelf Life in Healthy Adult Women

Published: 27-06-2019
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Main objective:To determine the bioequivalence of the hormones (ie, NGMN and EE) from the transdermal contraceptive patch using the newly sourced adhesive component N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48510

Source
ToetsingOnline

Brief title
Bioequivalence and adhesion study of EVRA patches

Condition

- Other condition

Synonym
Contraceptive

Health condition

Anticonceptie

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag International NV
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: Adhesion, Bioequivalence, EVRA, Transdermal

Outcome measures

Primary outcome

- To determine the bioequivalence of the hormones (ie, NGMN and EE) from the transdermal contraceptive patch using the newly sourced adhesive component Oppanol N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive component Oppanol B100 at BOSL.

- To evaluate the adhesion of the transdermal contraceptive patch using the newly sourced adhesive component Oppanol N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive component Oppanol B100 at BOSL.

Secondary outcome

To evaluate the irritation potential of the transdermal contraceptive patch using the newly sourced adhesive component Oppanol N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive component Oppanol B100 at

BOSL.

To assess the safety and tolerability of the transdermal contraceptive patch

using the newly sourced adhesive component Oppanol N100 at EOSL and the

currently marketed EVRA patch using the adhesive component Oppanol B100 at

BOSL.

Study description

Background summary

The compound being studied is called EVRA patch. EVRA is a contraceptive patch of 20 cm2 which is currently used worldwide to inhibit fertility. EVRA uses a 4 week (28 day) cycle during which for 3 consecutive weeks each week 1 patch will be worn, followed by 1 patch free week.

This study is designed to compare a test contraceptive patch with the currently marketed contraceptive patch (the EVRA patch). The only difference between the test patch and the EVRA patch is that 1 component of the adhesive of the patch (called Oppanol B100) is replaced by a similar component (Oppanol N100). All other components remain unchanged. For this study a test patch will be used that is about 2 years old, while the EVRA patch is about 4 months old at the start of the study .

The test patch and the EVRA patch both deliver the same combination of 2 hormones: 6 milligrams (mg) progestin (norelgestromin) and 600 micrograms (µg) estrogen (ethinyl estradiol).

The contraceptive test patch is not approved for use yet anywhere. The test patch was worn by 68 healthy female volunteers in a previous study. In that study a single 7-day application of the test contraceptive patch with the new adhesive component was safe and well tolerated.

Study objective

Main objective:
To determine the bioequivalence of the hormones (ie, NGMN and EE) from the transdermal contraceptive patch using the newly sourced adhesive component N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive component B100 at BOSL. To evaluate the adhesion of the transdermal contraceptive patch using the newly sourced adhesive component N100 at EOSL as

compared to the currently marketed EVRA patch using the adhesive component B100 at BOSL.

Secondary objectives:
To evaluate the irritation potential of the transdermal contraceptive patch using the newly sourced adhesive component N100 at EOSL as compared to the currently marketed EVRA patch using the adhesive component B100 at BOSL.
To assess the safety and tolerability of the transdermal contraceptive patch using the newly sourced adhesive component N100 at EOSL and the currently marketed EVRA patch using the adhesive component B100 at BOSL.

Study design

The study consists of 2 periods of 12 days. There will be a 21 day period between these two periods.

Intervention

The patch will be applied to the buttock while the subject is in a prone position, after which the patch will be removed 1 week later. The patch will be applied to an area that does not come in direct contact with the elastic of the clothing (e.g., underwear, sweat pants, or pajamas). There will be a period of 21 days between removal of the 1st patch in Period 1 and application of the 2nd patch in Period 2 (so for 3 weeks no hormonal anticonception will be given).

All volunteers in this study will wear once test patch and once the EVRA patch. In one period, a patch will be applied to the left buttock and in the other period a patch will be applied to the right buttock.

Study burden and risks

The study compound may cause side effects. The most commonly reported side effects of using hormonal contraception, such as EVRA, are headache, abdominal pain, nausea, vomiting, breast discomfort, bleeding between periods, emotional lability, and painful periods.

Other side effects reported with EVRA include redness, rash, itching, burning, hives, allergic reaction or swelling at the site of application. The most likely side effect from 7 days of patch wear is unexpected menstrual spotting or bleeding. Normal menses or periods should resume approximately 1 to 2 months after the study.

- Application and wearing of the patches: because each period is only 1-week, mild disruptions to the menstrual cycle may occur, such as delayed menses, breakthrough bleeding, or spotting. The bleeding usually starts on the second or third day after a patch is removed and will not always end by the day the

next period begins.
- The subject may expect the menstrual cycles to return to normal within 1 to 2 months after completing the study. The application of the patches for 2 times 1 week is not sufficient to prevent pregnancy. If applicable, it is important to use non-hormonal contraceptives (e.g., copper intrauterine device, unless the subject or her partner is surgically sterile).
- Measuring vital signs. There is generally no risk from taking body temperature, blood pressure, heart rate and respiratory rate. If the blood pressure is low during the measurement, then immediately standing up may cause the subject to feel dizzy and light headed. Thus, the subject may be at risk of losing your balance and falling. This side effect happens in normal people who don*t use any study compounds.
- To make a heart tracing (ECG), electrodes (small, plastic patches) will be pasted at specific locations on the arms, chest and legs. There is generally no risk with having an ECG. The sticky patches may pull the skin, or cause redness or itching.
- Taking blood and/or insertion of the indwelling cannula (tube in an arm vein) may (rarely) cause pain, bleeding, bruising or infection at the place where the needle goes into the skin. Similarly, the subject may feel dizzy or even faint during the procedure. The staff who take the blood will do all they can to keep these discomforts and risks to a minimum. The total amount of blood drawn during the study will be not more than approximatelt 230 milliliters.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject must be a woman of childbearing potential 18 to 45 years of age, inclusive, at screening
2. Subject has a body mass index (BMI) between 18 and 30 kg/m², inclusive, and body weight not less than 50 kg and not more than 100 kg at screening.
3. Subject must be healthy on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiogram (ECG) performed at screening. This determination will be recorded in the source documents and signed by the investigator.
4. Subject must have a negative serum (Beta-human chorionic gonadotropin [Beta-hCG]) pregnancy test at screening and a negative urine pregnancy test on Day -1 of each treatment period.
5. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol (see Section 4.4, Prohibitions and Restrictions).
6. Subject must be surgically sterile with intact ovaries, sexually abstinent, or, if sexually active with a non-sterilized male partner, be using a highly effective method (ie, failure rate of <1% per year) of nonhormonal contraception (eg, intrauterine device [IUD]) before admission until 1 month after completion of the study.
7. Subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study or within 1 month after completion of the study.
8. Each subject must sign an ICF indicating that she understands the purpose of, and procedures required for, the study, and is willing to participate in the study.
9. Subject has a blood pressure (measured in supine position, after at least 5 minutes rest in supine position) between 90 and 140 mmHg systolic, inclusive, and no higher than 90 mmHg diastolic at screening.
10. Subject has hematocrit of at least 36% at screening.
11. Subject must have a 12-lead ECG consistent with normal cardiac conduction and function at screening, including:
Normal sinus rhythm with heart rate between 45 and 100 beats per minute (bpm),

extremes included. QT interval corrected for heart rate (QTc) according to Fridericia's formula (QTcF)7 <=470 ms. QRS interval <=120 ms. PR interval <=220 ms. ECG morphology consistent with healthy cardiac conduction and function. Any evidence of heart block and left or right bundle branch block is exclusionary.
12. Subject must be a non-smoker, or an ex-smoker for >6 months, must not use nicotine-containing substances including tobacco products (eg, cigarettes, e-cigarettes, cigars, chewing tobacco, gum, patch), and tests negative for cotinine at screening and on Day -1 of each treatment period.

Exclusion criteria

1. Subject has a history of or current clinically significant medical illness including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood dyscrasias), lipid abnormalities, significant pulmonary disease, including bronchospastic respiratory disease, diabetes mellitus, renal or hepatic insufficiency, thyroid disease, neurologic or psychiatric disease, infection, cholelithiasis (gall stone disease), chronic idiopathic jaundice, family history of cholestatic jaundice, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the study results.
2. Subject has clinically significant abnormal values for hematology, biochemistry, or urinalysis at screening as deemed appropriate by the investigator.
3. Subject has abnormal thyroid stimulating hormone level at screening.
4. Subject has clinically significant abnormal 12-lead ECG, vital signs, or physical examination at screening as deemed appropriate by the investigator.
5. Subject has a history or presence of disorders commonly accepted as contraindications to sex hormonal therapy including, but not limited to, the following:
• Deep vein thrombophlebitis or thromboembolic disorders.
• Cerebral vascular or coronary artery disease, chronic untreated hypertension, or migraines.
• Benign or malignant liver tumor that developed during the use of oral contraceptives or other estrogen-containing products.
• Known or suspected estrogen-dependent neoplasia.
6. Subject has presence of disorders commonly accepted as contraindications to combined oral contraceptives including, but not limited to, the following:
• Undiagnosed abnormal vaginal bleeding.
• Any neurovascular lesion of the eye or serious visual disturbance.
• Any impairment of liver function or liver disease, or renal disease.
7. Subject has evidence of cervical dysplasia as documented by a CytoRich test or Papanicolaou (PAP) smear test within 10 months before screening. If a PAP smear has been done within 10 months prior to screening and results are available (documentation is available at the study site) a cervical smear does

not need to be performed.
8. Subject has used oral hormonal contraception, ie, contraceptive pills, within 3 months before admission to the study site on Day -1 of Treatment Period 1.
9. Subject currently has a contraceptive implant such as Implanon* or Norplant® in place, or has had removal of contraceptive implant within the 3 months before admission to the study site on Day -1 of Treatment Period 1.
10. Subject currently has a contraceptive vaginal ring such as NuvaRing® in place, or has had removal of contraceptive vaginal ring within the 3 months before admission to the study site on Day 1 of Treatment Period 1.
11. Subject received hormone injections such as Depo Provera® or deposubQ Provera 104, within the 3 months before admission to the study site on Day 1 of Treatment Period 1.
12. Subject used a steroid hormone-containing IUD such as Mirena® within the screening period from Day 28 until admission to the study site on Day 1 of Treatment Period 1.
13. Subject used any prescription or nonprescription medication (including herbal supplements), that are known CYP enzyme inducers or inhibitors (eg, St. John's Wort, cimetidine, or rifampin) within 30 days before the first patch application (Day 1 of Treatment Period 1). See Attachment 1 of the protocol for a list of medications that are known CYP enzyme inducers.
14. Subject used any prescription or nonprescription medication (including vitamins and herbal supplements), except for paracetamol, within 14 days before the first patch application is scheduled (Day 1 of Treatment Period 1).
15. Subject has a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V) criteria within 5 years before screening or positive test result(s) for alcohol or drugs of abuse (such as barbiturates, opiates, cocaine, amphetamines, methadone, benzodiazepines, methamphetamine, tetrahydrocannabinol, phencyclidine, and tricyclic antidepressants) at screening and on Day -1 of each treatment period. Note: A positive urine drug test, urine cotinine test, and/or alcohol breath test may be repeated once to exclude a technical error. Subjects with a negative urine drug, urine cotinine test, and/or alcohol breath test at retest may be included.
16. Subject has a known allergy to the study drug or any of the excipients of the formulation.
17. Subject has a known allergy to heparin or history of heparin induced thrombocytopenia.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-07-2019
Enrollment:	68
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	EVRA
Generic name:	ETHINYLESTRADIOL/NORELGESTROMIN Patch
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2019

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-001893-27-NL
ClinicalTrials.gov	NCT04017195
CCMO	NL70488.056.19

Study results

Date completed: 13-12-2019

Results posted: 09-12-2020

First publication
19-10-2020

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File