Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets

ethinylestradiol and dienogest

PL 20416/0461

Crescent Pharma Limited

LAY SUMMARY

Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets ethinylestradiol and dienogest

This is a summary of the Public Assessment Report (PAR) for Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Dienogest/Ethinylestradiol in this lay summary for ease of reading.

For practical information about using Dienogest/Ethinylestradiol, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Dienogest/Ethinylestradiol and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Valette 2.00 mg and 0.03 mg Film-coated tablet.

Dienogest/Ethinylestradiol is:

- used to prevent pregnancy (contraceptive "pill")
- used for treatment of women with moderate acne, who agree to receive a contraceptive pill after failure of suitable local or oral antibiotic treatments

How does Dienogest/Ethinylestradiol work?
Each of the tablets contains a small amount of two different female hormones, ethinylestradiol and dienogest. Contraceptive pills that contain two hormones are called "combined pills" or "combined hormonal contraceptives". In women experiencing acne as a result of a marked effect of male hormones (known as "androgens"), clinical trials have proven that Dienogest/Ethinylestradiol leads to an improvement in these symptoms.

How is Dienogest/Ethinylestradiol used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The patient should take one tablet of Dienogest/Ethinylestradiol every day.

The tablet should be swallowed whole, with a small amount of water if necessary.

The tablet may be taken with or without food, but the patient should take the tablet at around the same time every day.

One blister contains 21 coated tablets. Next to each tablet is printed the day of the week that it should be taken. The patient should take one tablet marked with that day of the week. If, for example the patient starts on Friday, they should take a tablet with Fr (for Friday) next to it, by pressing it through the aluminium foil. The patient should take one tablet every day, according to the sequence. The time of day does not matter, but the patient should stick to this time once selected.

The patient should follow the direction of the arrow on the blister until all 21 tablets have been taken. Then, the patient should take no tablets for 7 days. In the course of this 7 tablet free days, the patient's monthly period (withdrawal bleeding) should occur 2-3 days after taking the last tablet.

On the 8th day after the last Dienogest/Ethinylestradiol tablet (that is, after the 7-day gap week), the patient should start with the following blister, whether their bleeding has stopped or not. This means that the patient will start every new blister on the same day of the week, and that the withdrawal bleed should occur on the same days every month.

If the patient uses Dienogest/Ethinylestradiol in this manner, they are also protected against pregnancy during the 7 days when they are not taking the Dienogest/Ethinylestradiol tablet.

For further information on how Dienogest/Ethinylestradiol is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Dienogest/Ethinylestradiol have been shown in studies?
Because Dienogest/Ethinylestradiol is a generic medicine, studies in healthy volunteers have been limited to tests to determine that it is bioequivalent to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Dienogest/Ethinylestradiol?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Dienogest/Ethinylestradiol is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are considered to be the same as the reference medicine.

Why was Dienogest/Ethinylestradiol approved?
It was concluded that, Dienogest/Ethinylestradiol has been shown to be comparable to and to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

Dienogest/Ethinylestradiol has been authorised with the condition to perform further studies and/or to provide additional measures to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Dienogest/Ethinylestradiol?"

What measures are being taken to ensure the safe and effective use of Dienogest/Ethinylestradiol?

As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Dienogest/Ethinylestradiol. The RMP details the important risks of Dienogest/Ethinylestradiol, how these risks can be minimised, any uncertainties about Dienogest/Ethinylestradiol (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Dienogest/Ethinylestradiol:

Important identified risks	• Venous thromboembolism • Arterial thromboembolism
Important potential risks	• None
Missing information	• None

Educational materials for healthcare professionals (a prescriber checklist) and patients (a patient information card and Q&A document) will be provided to address the risks of arterial thromboembolism and venous thromboembolism.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Dienogest/Ethinylestradiol are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Dienogest/Ethinylestradiol

A marketing authorisation for Dienogest/Ethinylestradiol was granted in the United Kingdom (UK) on 09 January 2024.

The full PAR for Dienogest/Ethinylestradiol follows this summary.

This summary was last updated in February 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets (PL 20416/0461) could be approved.

The product is approved for the following indications:

- Oral contraception.
- Treatment of moderate acne after failure of suitable topical treatments or oral antibiotic treatment in women who elect to use an oral contraceptive.

The decision to prescribe Dienogest/Ethinylestradiol should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Dienogest/Ethinylestradiol compares with other combined hormonal contraceptives.

This product is an effective antiandrogen compound for oral contraception, consisting of the estrogen ethinylestradiol and the progestogen dienogest.

The contraceptive effect of dienogest/ethinylestradiol is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and changes in cervical secretion.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Valette 2.00 mg and 0.03 mg Film-coated tablet, that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets was granted in the United Kingdom (UK) on 09 January 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of film-coated tablets. Each film-coated tablet contains 0.03 mg of ethinylestradiol and 2.0 mg of dienogest.

In addition to ethinylestradiol and dienogest, this product also contains the following excipients:

Tablet core
Lactose monohydrate
Magnesium stearate
Maize starch
Povidone K-30

Film coating
Hypromellose 2910
Polyethylene Glycol
Titanium dioxide (E171)

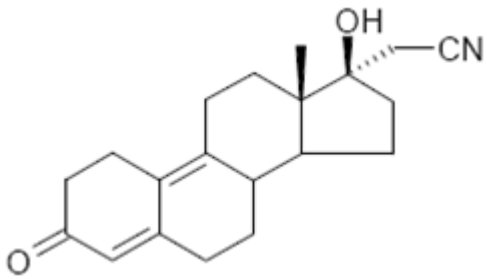
The finished product is packaged in PVC/PVDC/Aluminium blister in pack sizes of 21, 3 x 21 and 6 x 21 film-coated tablets. The blister packs may come with a blister holder. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCES

rINN: Dienogest

Chemical Name: (17α)-17-hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile
Molecular Formula: $C_{20}H_{25}NO_2$
Chemical Structure:

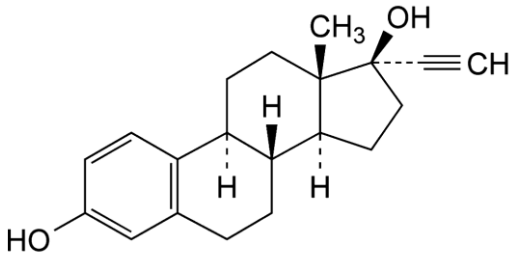


Molecular Weight: 311.4
Appearance: White, almost white or slightly yellow, crystalline powder
Solubility: Practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in methanol.

Dienogest is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Ethinylestradiol
Chemical Name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
Molecular Formula: $C_{20}H_{24}O_2$
Chemical Structure:



Molecular Weight: 296.4
Appearance: White or slightly yellowish-white, crystalline powder.
Solubility: Practically insoluble in water, freely soluble in ethanol (96 per cent). It dissolves in dilute alkaline solutions.

Ethinylestradiol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* dissolution profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'Do not store above 30ºC. Store in the original package', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of ethinylestradiol and dienogest are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of ethinylestradiol and dienogest are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study.

Bioequivalence study 1

This study was a randomised, two period, crossover, open-label, single-dose, comparative bioavailability study comparing the test product, Dienogest/Ethinylestradiol 2.0/0.03 mg film-coated tablets, versus the reference product Valette 2.0 mg/0.03 mg Film-coated tablet, in healthy subjects under fasting conditions.

After an overnight fast of at least 10 hours, subjects were administered test or reference product. Blood samples were taken pre-dose and up to 60 hours post dose for dienogest and up to 72 hours post dose for ethinylestradiol, with a washout period of 28 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

Analyte: Dienogest (N = 26)

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	CV(%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_{0-t} *(ng*h/mL)*	A	602.19	24	585.46	A vs. B	99.96	97.01	- 102.99	6
	B	602.40	25	585.72					
Cmax *(ng/mL)*	A	56.45	25	54.81	A vs. B	102.79	96.47	- 109.54	13
	B	54.30	19	53.32					
AUC_{0-inf} *(ng*h/mL)*	A	629.06	24						
	B	627.21	24						
Tmax *(h)*	A	1.06	50						
	B	1.33	47						
Kel *(1/h)*	A	0.0666	21						
	B	0.0687	19						
Thalf *(h)*	A	10.85	21						
	B	10.45	19						

Analyte: Ethinyl estradiol (N = 26)

Parameter	TRT	Means			Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Arithmetic	CV(%)	Geometric			Lower	Upper	
Based on Measured Data									
AUC_{0-t} *(pg*h/mL)*	A	761.616	26	737.265	A vs. B	101.14	96.82	- 105.66	9
	B	754.450	27	728.920					
Cmax *(pg/mL)*	A	70.446	30	67.752	A vs. B	102.11	96.95	- 107.55	11
	B	68.442	25	66.351					
AUC_{0-inf} *(pg*h/mL)*	A	795.503	27						
	B	789.516	27						
Tmax *(h)*	A	1.29	26						
	B	1.47	25						
Kel *(1/h)*	A	0.0439	16						
	B	0.0453	16						
Thalf *(h)*	A	16.21	17						
	B	15.72	17						

Bioequivalence conclusion

Dienogest

Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Lower	Upper	
A vs. B	99.96	97.01	- 102.99	6
A vs. B	102.79	96.47	- 109.54	13

Ethinyl estradiol

Contrast	Ratio	90% CI		Intra-Sub CV(%)
		Lower	Upper	
A vs. B	101.14	96.82	- 105.66	9
A vs. B	102.11	96.95	- 107.55	11

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional risk minimisation measures have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for all safety concerns):

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Venous thromboembolism	**Routine risk minimisation measures:** Routine risk communication: SmPC sections 4.1, 4.3, 4.4, 4.6 and 4.8 PL section 2 and 4 Pack size: *21, 3x21 and 6x21 film-coated tablets* Legal status: *Medical prescription* **Additional risk minimisation measures:** Checklist for prescribers Patient information card Questions and answers on Dienogest/Ethinylestradiol 2.0/ 0.03 mg film-coated tablets: latest information for women	None

Arterial thromboembolism	**Routine risk minimisation measures:** Routine risk communication: SmPC sections 4.3, 4.4, 4.6 and 4.8 PL section 2 and 4 Pack size: *21, 3x21 and 6x21 film-coated tablets* Legal status: *Medical prescription* **Additional risk minimisation measures:** Checklist for prescribers Patient information card Questions and answers on Dienogest/ Ethinylestradiol 2.0/0.03mg film-coated tablets: latest information for women	None

This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ethinylestradiol and dienogest is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**