**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Floridon 150 micrograms/30 micrograms film-coated tablets
Levonorgestrel
Ethinylestradiol
PA1330/031/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Floridon 150 micrograms/30 micrograms film-coated tablets, from Gedeon Richter Plc. on 15th November 2024 for oral contraception .

This national application concerns a generic version of Levonorgestrel Ethinylestradiol 150 micrograms/30 micrograms tablets, under the trade name Stediril 30 150 micrograms/30 micrograms Pfizer BV and the application is made under article 10(1).

The IE reference product is Ovranette 150 micrograms/30 micrograms marketed by Pfizer Healthcare Ireland.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

| | |
|---|---|
| Name of the product: | Floridon 150 micrograms/30 micrograms film-coated tablets |
| Name(s) of the active substance(s) (INN): | Levonorgestrel and Ethinylestradiol |
| Pharmacotherapeutic classification (ATC code) | G03FA11 |
| Pharmaceutical form and strength(s) | 150 micrograms/30 micrograms film-coated tablet |
| Marketing Authorisation Number(s) in Ireland (PA) | PA1330/031/001 |
| Marketing Authorisation Holder | Gedeon Richter Plc. |

## II. QUALITY ASPECTS

### II.1. Introduction
This application is for Floridon 150 micrograms/30 micrograms film-coated tablets.

### II.2 Drug substance
The active substances are levonorgestrel and ethinylestradiol, established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with the specifications has been provided.

### II.3 Medicinal product
P.1 Composition
The product contains 150 micrograms of levonorgestrel and 30 micrograms of ethinylestradiol.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with the Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Floridon 150 micrograms/30 micrograms film-coated tablets.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance is a generic formulation of Stediril 30 on the European market since 1974. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of Levonorgestrel / Ethinylestradiol are well known.

**III.2 Ecotoxicity/environmental risk assessment**

Levonorgestrel / Ethinylestradiol pose a risk to the aquatic environment. Since Floridon is intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

**III.3 Discussion on the non-clinical aspects**

The pharmacodynamic, pharmacokinetic and toxicological properties of Levonorgestrel / Ethinylestradiol are well known. As Levonorgestrel / Ethinylestradiol are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. A nonclinical overview based on literature review is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

## IV. CLINICAL ASPECTS

**IV.1 Introduction**

Levonorgestrel + Ethinylestradiol 0.15 mg/0.03 mg film-coated tablets are low-dose, combined, monophasic oral contraceptive. Its active ingredients are the well-known ethinylestradiol and levonorgestrel.

The therapeutic indication is 'oral contraception' as per the SmPC.
One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval during which time a withdrawal bleed usually occurs.

The method of administration is clearly outlined in section 4.2 of the SmPC including instructions on switching OCP, starting post abortion and commencing use postpartum. There is further instruction given regarding missed doses and delaying periods.

There are numerous contraindications to use which are as follows:

Oral contraceptives should not be used in women with any of the following conditions. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately:

- Venous thrombosis present or in history (deep vein thrombosis, pulmonary embolism)
- Arterial thrombosis present or in history (e.g. myocardial infaraction)
- Thrombophlebitis or thromboembolic (arterial or venous) disorders or other diseases, associated with an increased thromboembolic risk such as thrombogenic valvulopathies and thrombogenic rhythm disorders (current or history)
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4)
- Hereditary or acquired predisposition for venous or arterial thrombosis (see section 4.4)
- Cerebrovascular accident or coronary artery disease present or in history
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Hepatic adenomas or carcinomas, or severe liver disease, current or previous, as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Pancreatitis associated with severe hypertriglyceridaemia (current or history)
- Uncontrolled hypertension
- Diabetes mellitus with vascular involvement
- History of migraine with focal neurological symptoms, such as aura
- Known or suspected pregnancy
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

This is clearly noted in the SmPC in section 4.3.

Interactions with other medicinal products is detailed clearly in section 4.5 of the SmPC.

**IV.2 Pharmacokinetics**

Ethinylestradiol is rapidly and well absorbed from the gastrointestinal tract but is subject to first pass metabolism in the gut wall. Compared to other estrogens it is only slowly metabolised in the liver. Excretion is via the kidneys with some appearing also in the faeces.
Levonorgestrel is absorbed from the gastrointestinal tract. Metabolites are excreted in the urine and faeces as glucuronide and sulphate conjugates.

**IV.3 Pharmacodynamics**

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens and estrogens, fixed combinations.
ATC code: G03FA11

Floridon is a combined oral contraceptive (COC) containing the estrogen ethinylestradiol and the progestogen, levonorgestrel. COCs have been shown to exert their effect by decreasing gonadotropin secretion to suppress ovarian activity.

The resulting contraceptive effect is based on various mechanisms, the most important of which is the inhibition of ovulation.

**IV.4 Clinical Efficacy**

No new clinical efficacy data was submitted.

**IV.5 Clinical Safety**

A Risk Management Plan, version 0.2, dates 31 May 2023, has been submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Floridon. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Periodic Safety Update Reports (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

No new clinical safety data was submitted with this application. The safety profile of this product is stated in the SmPC.

**IV.6 Discussion on the clinical aspects**

To support the application, the applicant has submitted one bioequivalence study.
The submitted study is a Randomized, Open-Label, 2-Stage, 2-Way Crossover Bioequivalence Study of Levonorgestrel + Ethinylestradiol 0.15 mg/0.03 mg Film-Coated Tablet and Stediril 30 (Reference) Following a 0.15 mg/0.03 mg Dose in Healthy Subjects Under Fasting Conditions. This was conducted in line with the EMA bioequivalence guidelines (CPMP/EWP/QWP/1401/98). No deaths, serious or significant AEs were reported during this study.

**V. OVERALL CONCLUSIONS**

The efficacy and safety profile of Levonorgestrel + Ethinylestradiol 0.15 mg/0.03 mg is established, and this combination is used as effective combined oral contraception.
This application contained an adequate clinical overview and bioequivalence has been shown.
The safety aspects including contraindications and drug interactions is clearly outlined in the SmPC. The benefit risk is considered positive.

**VI. REVISION DATE**

**VII. UPDATES**

This section reflects the significant changes following finalisation of the initial procedure.

| SCOPE | PROCEDURE NUMBER | PRODUCT INFORMATION AFFECTED | DATE OF START OF PROCEDURE | DATE OF END OF PROCEDURE |
|---|---|---|---|---|
| New National | CRN00DJRL | SmPC, IPAR, PIL & Label | 15th November 2024 | 14th November 2029 |