CMDh/223/2005
February 2014

Public Assessment Report

Scientific discussion

Estradiol Besins 1 mg film-coated tablets
Estradiol Besins 2 mg film-coated tablets
(Estradiol hemihydrate)

ES/H/0914/001-002/DC

Date: 30/04/2025

This module reflects the scientific discussion for the approval of Estradiol Besins. The procedure was finalised at 02/01/2025. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Estradiol Besins 1mg and 2 mg film-coated tablets, from Laboratorios Cinfa S.A.

Estradiol 1 mg film-coated tablets indicated in:

- Hormone Replacement Therapy for oestrogen deficiency symptoms in postmenopausal women.

Estradiol 2 mg film-coated tablets indicated in:

- Hormone Replacement Therapy for oestrogen deficiency symptoms in postmenopausal women.
- Prevention of osteoporosis in postmenopausal women at high risk of future fractures, who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application which has been granted pursuant to Article 10.1 of Directive 2001/83/EC, claiming essential similarity with the innovator products Estrofem 1 mg/ 2 mg comprimés pelliculés which have been registered in EU, Belgium, by Novo Nordisk Pharma since 02/12/1997-18/12/1991.

In this procedure the concerned member states have been CZ, DE, DK, FI, PL, SE and SK.

II. QUALITY ASPECTS

II.1 Introduction

The product Estradiol Besins 1 mg film-coated tablets consists on red-coloured, round, biconvex film-coated tablets containing 1 mg of Estradiol.
The product Estradiol Besins 2 mg film-coated tablets consists on blue-coloured, round, biconvex film-coated tablets containing 2 mg of Estradiol.
The maximum daily dose is 2 mg of Estradiol.
Estradiol Besins 1 mg film-coated tablets and Estradiol Besins 2 mg film-coated tablets are packaged in blister packs consisting of polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVDC) blisters heat-sealed with aluminum (Alu) foil.

II.2 Drug Substance

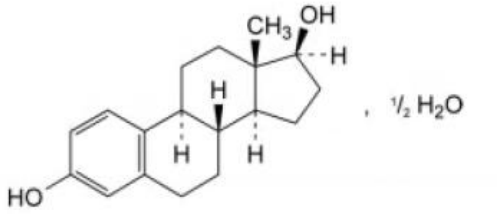
The CEP procedure is used to support the quality of the drug substance.

General Information

Nomenclature:

INN: Estradiol hemihydrate
Chemical name: Estra-1,3,5(10)-triene-3,17β-diol
CAS: 35380-71-3

Chemical structure:



Empirical Formula: $C_{18}H_{24}O_2$. 0.5 H_2O
Molecular weight: 281.39 g/mol

General Properties:

Appearance: White to off-white crystalline powder
Solubility: Practically insoluble in water, very slightly soluble in ethanol, soluble in acetone, insoluble in dichloromethane and diethylether.
Polymorphism: An anhydrous as well as a hemi hydrated form are known for Estradiol. Various morphologies of polymorphs of a steroid are observed. The producer consistently manufactures the more stable polymorphic form which is Estradiol hemihydrate.
Chirality: Estradiol contains five asymmetric carbon centers which are shown in the structure above. As final drug substance the β-Isomer is used.
Melting point: 175 - 180 °C.
Hygroscopicity: Not hygroscopic.
Optical rotation: +76.0 to + 83.0°

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

Description of the product

The product Estradiol Besins 1 mg film-coated tablets consists on red-coloured, round, biconvex film-coated tablet marked with "E1" on one side and without marking on the other side, with a diameter of approximately 6 mm, containing 1 mg of Estradiol.
The product Estradiol Besins 2 mg film-coated tablets consists on blue-coloured, round, biconvex film-coated tablet marked with "E2" on one side and without marking on the other side, with a diameter of approximately 6 mm, containing 2 mg of Estradiol.
The qualitative composition of the finished product is as follows:

1 mg tablet	2 mg tablet
Tablet core	*Tablet core*
Estradiol hemihydrate	Estradiol hemihydrate
Lactose monohydrate	Lactose monohydrate
Maize starch	Maize starch
Hypromellose	Hypromellose
Magnesium stearate	Magnesium stearate
Coating	*Coating*
Opadry II red:	Opadry II blue:
Polyvinyl alcohol	Polyvinyl alcohol
Macrogol	Macrogol
Titanium dioxide	Titanium dioxide
Talc	Talc
Iron oxide red	FD&C Blue

The packaging material intended for the commercial use consists in blister packs consisting of polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVDC) blisters heat-sealed with aluminum (Alu) foil.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.
Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin, except for the case of lactose, obtained from milk for human consumption.

Scientific data and/or certificates are presented to guarantee compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents* for these excipients.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVDC) blisters heat-sealed with aluminum (Alu) foil. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 24 months.

Storage conditions: This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of estradiol hemihydrate are well known. As estradiol hemihydrate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Environmental Risk Assessment (ERA)

Since Estradiol Goibela 1 mg and 2 mg film-coated tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Estradiol is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 2 mg strength according to the Guideline on the investigation of bioequivalence, which is discussed below.

IV.2 Pharmacokinetics

Biowaiver

This application concerns two strengths, i.e., 1 and 2 mg film-coated tablets and the bioequivalence study has been carried out with the 2 mg strength.

The criteria according to the Guideline on the Investigation of Bioequivalence for waiving the 1 mg tablets are fulfilled as:

- The two strengths are manufactured with the same process.
- The qualitative composition of the two strengths is the same.
- The composition of the strengths is quantitatively proportional.
- Appropriate dissolution profiles between the different strengths have confirmed to be similar.

Bioequivalence studies

Study code

259-21

GCP compliance

The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities

Clinical site: AXIS Clinicals Limited. Atharva, Opp Rajpath club, S. G. Highway, Bodakdev, Ahmedabad-380054, Gujarat, India

Analytical centre: AXIS Clinicals Limited. 1-121/1, Sy. Nos. 66 (Part) & 67 (Part), Miyapur, Serilingampally, Hyderabad – 500049, Telangana, India.

Design.

A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 52 healthy female volunteers, aged 45– 65 years. Each subject received a single dose (2 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 10 days.

Analytical and statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.

The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00% for baseline-adjusted Estrone (total) and, as supportive data, estradiol (unconjugated) and estrone (unconjugated).

The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
52 subjects were included in the study. 52 subjects were treated, 50 subjects completed the study and 49 were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters for <u>baseline corrected total estrone</u> (non-transformed values; arithmetic mean ± SD)

Treatment	**AUC_{0-t}** **ng/ml/h**	**C_{max}** **ng/ml**
Test	197.73	35.78
Reference	193.63	32.54
***Ratio (90% CI)**	102.11 (99.46-104.84)	109.93 (103.42-116.86)

C_{max} Maximum plasma concentration
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

*ln-transformed values

Table 2. Pharmacokinetic parameters for <u>baseline corrected estradiol</u> (non-transformed values; arithmetic mean ± SD)

Treatment	**AUC_{0-t}** **pg/ml/h**	**C_{max}** **pg/ml**
Test	1055.33	43.69
Reference	1039.57	39.43
***Ratio (90% CI)**	101.52 (92.94-110.89	110.82 (97.18-126.37)

C_{max} Maximum plasma concentration
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

*ln-transformed values

Table 3. Pharmacokinetic parameters for baseline corrected estrone unconjugated (non-transformed values; arithmetic mean ± SD)

Treatment	AUC_{0-t} pg/ml/h	C_{max} pg/ml
Test	8882.18	553.56
Reference	8769.34	509.35
***Ratio (90% CI)**	101.296 (97.37-105.36)	108.66 (103.70-113.85)

C_{max} Maximum plasma concentration
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.

*ln-transformed values

In this case, Cmax of the parent compound may not be the most sensitive parameter to detect formulation differences given the quick and almost complete metabolism for estradiol, it is not possible to distinguish a first absorption peak. However, the plasma profile of estrone is characterized by an earlier, higher and more distinct peak and reflects the performance of the formulation better than estradiol Cmax.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Estradiol Goibela 2 mg film-coated tablets are considered bioequivalent with Estrofem 2 mg film-coated tablets.

The results of study 259-21 with 2 mg formulation can be extrapolated to other 1 m strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics, Clinical efficacy and Clinical safety

No new clinical data have been provided and none is required for this type of generic application.

The submitted clinical documentation based on scientific literature is sufficient and acceptable regarding clinical information.

IV.4 Risk Management Plan

The MAH has submitted a risk management plan, 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 Estradiol Besins 1 mg and 2 mg film-coated tablets (estradiol hemihydrate).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Estradiol Besins 1 mg and 2 mg film-coated tablets (estradiol hemihydrate).

IV.5 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Estradiol Goibela is found adequate. There are no objections to the approval of Estradiol Goibela 1, and 2 mg film coated tablets from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

The results of the study with the 2 mg strength can be extrapolated to the 1 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.