

Module 2.5

Clinical Overview Addendum Besins Healthcare

Estradiol Gel (Oestrogel / Estrogel)

July 2024

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List of abbreviations and definitions of terms

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical code
ALT	Alanine aminotransferase liver enzyme
BMS	British Menopause Society
BNF	British National Formulary
CCDS	Core Company Data Sheet
CHC	Combined Hormonal Contraceptive
CHMP	Committee for Human Medicinal Products
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human
CSI	Company Core Safety Information
DLP	Data lock point
E2	Estradiol
EEA	European Economic Area
EMA	European Medicines Agency
E2	Estradiol
EU	European Union
FDA	Food and Drug Administration
g	gramme
H	Hydrogen
HCV	Hepatitis C virus
HRT	Hormone Replacement Therapy
iDAP	Drug Analysis Profiles
LH	Luteal Hormone
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	micrograms
MHRA	Medicines and Healthcare products Regulatory Agency
NAMS	North American Menopause Society
NICE	National Institute of Clinical Excellence
O	Oxygen
PBRER	Periodic Benefit-Risk Evaluation Reports
Ph Eur	European Pharmacopoeia
PI	Product Information
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PSUSA	Periodic Safety Update Single Assessment
QRD	EMA Working Group on Quality Review of Documents
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SOC	System Organ Class
US /USA	United States of America
ULN	Upper Limit of Normal

INTRODUCTION

This Clinical Overview Addendum provides an overview of the evidence in support of the proposed safety labelling updates to the Product Information for Estradiol Gel / Oestrogel / Estrogel – referred to within this document as ‘Estrogel’. For information on the biopharmaceutics, pharmacology and efficacy, reference should be made to relevant sections of the currently approved Clinical Overview.

Overview of the Product Information

The Estradiol Gel is a transdermal gel formulation known under the trade names Oestrogel®, Oestrodose®, Estradiol gel® and Estrogel safety®, and is referred to in this document as Estrogel.

The product information of Estrogel has been assessed on a global scale and is being updated to align the information intended for healthcare professionals and patients with the latest scientific conclusions and available product data.

Estrogel is indicated for use in postmenopausal women for:

- Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms, (in women at least six months since last menses), and
- 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.

The product is available in Europe in two pack types:

A conventional plastic tube containing either 30 g or 80 g of estradiol 0.06% gel, and a plastic spatula to help measure a minimum 1.25 g dose, equivalent to 0.75 mg estradiol.

A plastic bottle with metering valve (pump pack) that delivers 1.25 g of 0.06% gel, equivalent to 0.75 mg of estradiol.

The formulation is indicated for women without a uterus. In women with an intact uterus consideration should be given to the addition of a progestogen, including micronised progesterone, for at least 12 to 14 days every month / 28-day cycle, to reduce the risk of endometrial hyperplasia and carcinoma.

For the treatment of postmenopausal symptoms, the dosage varies according to individual need. The minimum effective dose of 1.25 g of gel per day (equal to 0.75 mg of estradiol) is recommended for 21 to 28 days per month/ 28-day cycle. The mean dose is 2.5 g of gel per day. For treatment of menopausal symptoms, the lowest effective dose should be used for the shortest possible time.

Progestogen dosing should be in accordance with the doctor’s prescription, as outlined in the approved Product Information for progestogens. Only progestogens approved for combination use with oestrogen treatment should be recommended.

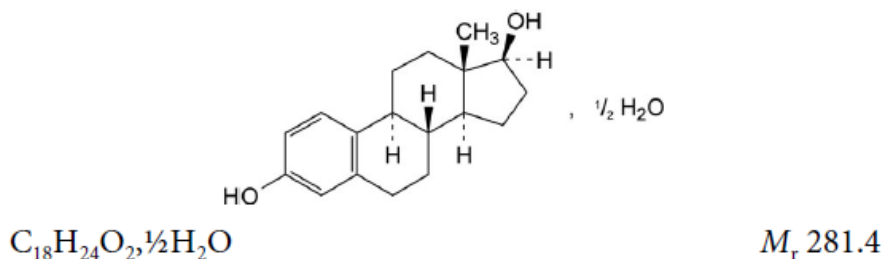
Experience with treating women older than 65 years is limited. No pharmacokinetic (PK) studies have been conducted in special populations, including patients with renal or hepatic impairment.

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Estradiol (also known as E2, β -Estradiol, 17 β -Estradiol, or Oestradiol, Figure 1 17 β -Oestradiol) is a naturally occurring steroid reproductive hormone and the major female sex hormone in women. It has been used for decades for contraception and for the treatment of various forms of oestrogen deficiency. Consequently, there is a large pool of human safety experience with this hormone.

The overall extent of human exposure to transdermal or oral estradiol, including the Besins estradiol formulations, is such that the available clinical safety data render what is reported from nonclinical studies of limited relevance. The information presented in this Clinical Overview Addendum considers human data primarily taken from key publications and product information guidance from relevant scientific bodies.

Figure 1: Molecular Structure and Definitions: Estradiol Hemihydrate
(Ph Eur 2024)



Estradiol was identified more than 80 years ago as the major oestrogenic hormone secreted by the human ovary [REDACTED]. It is naturally produced for three out of 30 days of the menstrual cycle. It represents the major oestrogen in humans [REDACTED].

The three main natural oestrogens in women are estradiol, estrone and estriol, of which estradiol has the highest oestrogenic activity [REDACTED]. Estradiol is the predominant form in non-pregnant women in their reproductive years. During pregnancy estriol predominates and estrone is the main form in postmenopausal women [REDACTED].

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

Not applicable

2.5.4 OVERVIEW OF EFFICACY

Not applicable.

2.5.5 OVERVIEW OF SAFETY

2.5.5.1 Introduction

As might be expected for a naturally occurring hormone that has been widely used for contraception and treatment of hormone deficiency and other conditions, the safety profile of estradiol in pharmaceutical formulations is very well established [REDACTED]. Estradiol has been used in clinical practice for decades and this is reflected in the significant pool of published information on its safe use. Compared with other hormones in its class, estradiol has a comparable or more favourable safety profile when administered transdermally ([NICE 2019](#)).

The estradiol clinical safety database includes information relating to use of various oestrogen types, formulations, and administration routes in different clinical indications and settings, including evidence for from published reports, PSURs/PBRERs, postmarketing surveillance data from the UK MHRA on all formulations containing estradiol, and from the US FDA ([EstroGel USPI 2020](#), [REDACTED] [iDAP 2024](#)).

Class labelling has been introduced in the EU for oestrogens in HRT. Currently there is an EU Core Summary of Product Characteristics (SmPC) and a Product Information Leaflet (PIL) for medicines intended for the treatments for menopause and related symptoms ([Core SmPC for HRT 2023](#)). This class labelling mandates much of the structure and safety of the product information, and includes specific wording, warnings, and precautions.

In addition, the following EU mandatory templates, guidelines, and national regulatory agency mandated wording affects structure and content of product information in the EU:

- The QRD (Quality Review of Documents) template – which provides headings and the structure of mandatory statements in the product information and labelling,
- Annex 1 to the European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ (SANTE-2017-11668) ([EMA 2019](#)),
- Mandatory statements from the EU Pharmacovigilance Risk Assessment Committee (PRAC),
- Other mandated safety statements – for example from the UK MHRA and other regulatory agencies.

2.5.5.2 Exposure

Estradiol has been clinically available worldwide for more than 50 years and clinical experience with the drug substance in women of all ages is extensive [REDACTED]

Estrogel was first introduced for clinical use in France in 1974.

Currently the product is approved in more than 70 countries worldwide.

2.5.5.3 Adverse Events

There are significant clinical safety data available to support use of topical / transdermal oestrogen in the approved indications. [REDACTED]

The overall safety profile of Estrogel is well established and the product is well tolerated at the recommended therapeutic dose.

Common undesirable effects include headache, nausea, abdominal pain, breast swelling/pain, breast enlargement, dysmenorrhoea, menorrhagia, metrorrhagia, leucorrhoea discharge, endometrial hyperplasia, weight change (increase or decrease), and water retention with peripheral oedema [REDACTED]

[REDACTED] [BNF Estradiol 2024](#), [iDAP 2024](#)). These are all noted within the prescribing information – See 2.5.5.6 Proposed changes to the Product Information Section 4.8 Undesirable Effects for further details.

2.5.5.4 Methodology

Following a review of relevant safety data, the Product Information (PI) (also referred to as the Summary of Product Characteristics (SmPC)) is proposed updated.

All relevant company generated safety data have been reviewed, along with company and comparator labelling from main regions, including the EEA. Literature reviews have been conducted, along with a review of standard reference medical textbooks and reference texts, to identify additional relevant safety information.

The proposed updates to the product information are described in the following section. These include mandatory EU Quality Review of Documents (QRD) changes and formatting changes to improve readability.

Only those sections of the PI for which changes have been implemented are outlined below:

- Newly proposed information is underlined.
- Deleted text is shown as ~~striketrough~~.
- Proposed relocations of safety information are *italicized*.

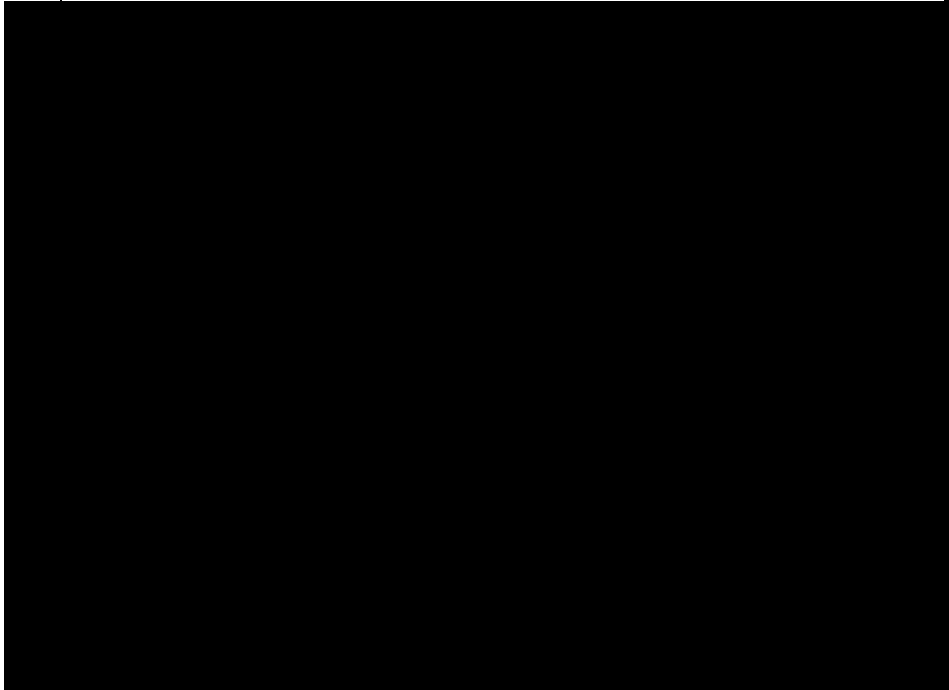
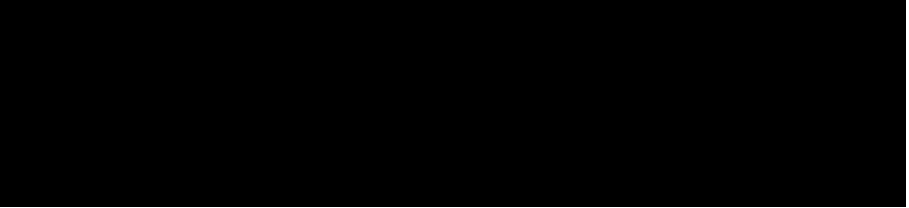
2.5.5.5 Proposed changes to the Product Information

Tabulations of the proposed changes and the rationale for each change are presented overleaf.

Section 4.2: Posology and method of administration

Proposed amendment	Rationale
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used. The lowest effective dose for the prevention of osteoporosis is not known.	This statement is mandated in the EU Core SmPC for HRT (latest version – May 2023) and is derived from the EU PRAC. (Core SmPC for HRT 2023). Using a higher dose than the lowest effective dose or using the product at or above the lowest effective dose for longer than necessary could have a detrimental impact on safety.
In women with a uterus consideration should be given to the addition of a progestagen including progesterone for at least 12 to 14 days every month / 28-day cycle to reduce the risk of endometrial hyperplasia and carcinoma.	
Patients should be informed that children should not come in contact with the area of the body where estradiol gel has been applied (see Section 4.4)	
Estradiol Gel should NOT be applied on or near the breasts or on the vulval region.	
Secondary exposure to estradiol can potentially occur as a result of passive transfer following skin-to-skin contact.	
<i>Paediatric population</i> There is no relevant use of Estrogel in children aged less than 12 years	

Section 4.3: Contraindications

Proposed amendment	Rationale
	

Section 4.4 Special warnings and precautions for use

Proposed amendment	Rationale

Proposed amendment	Rationale

Proposed amendment	Rationale

Section 4.5: Interaction with other medicinal products and other forms of interaction

	Rationale

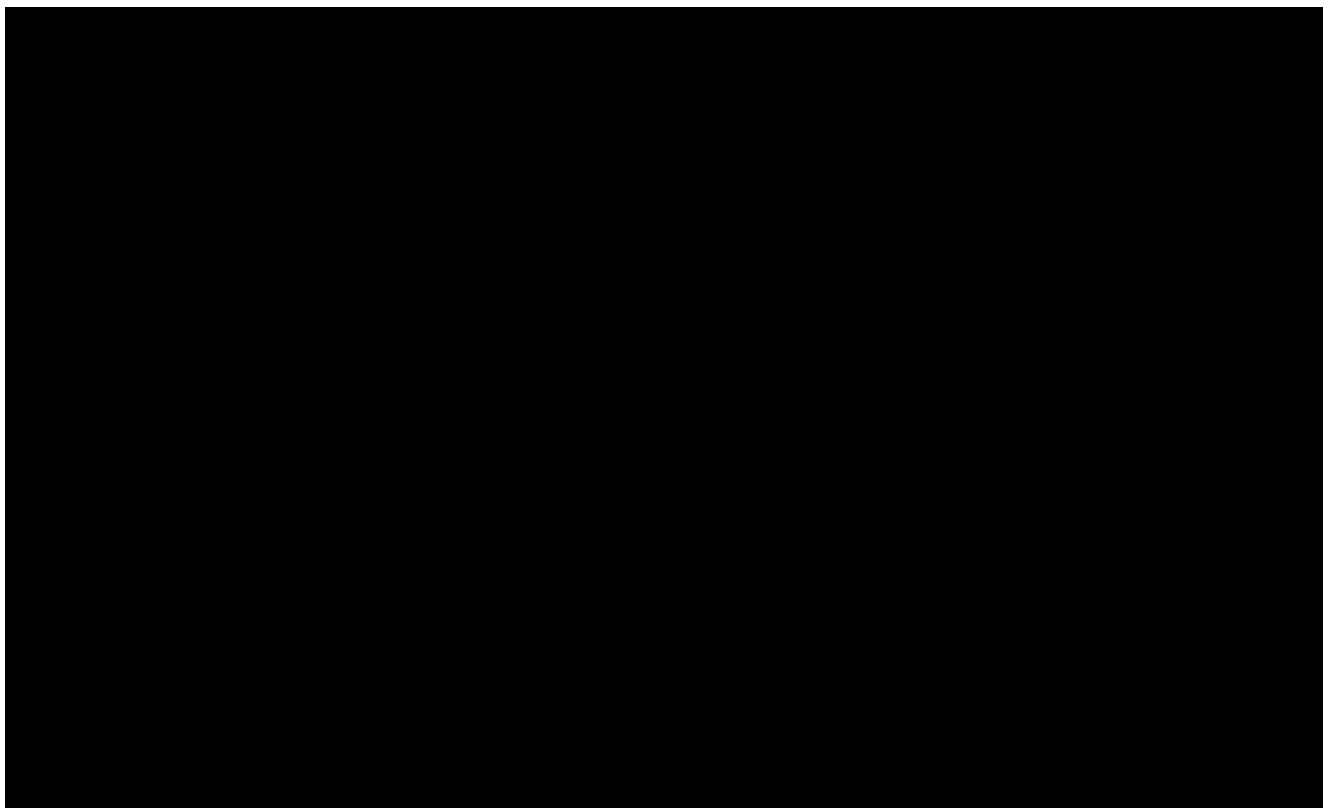
Proposed amendment	Rationale
	

Section 4.6: Fertility, Pregnancy and Lactation

Proposed amendment	Rationale
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Section 4.8: Undesirable effects

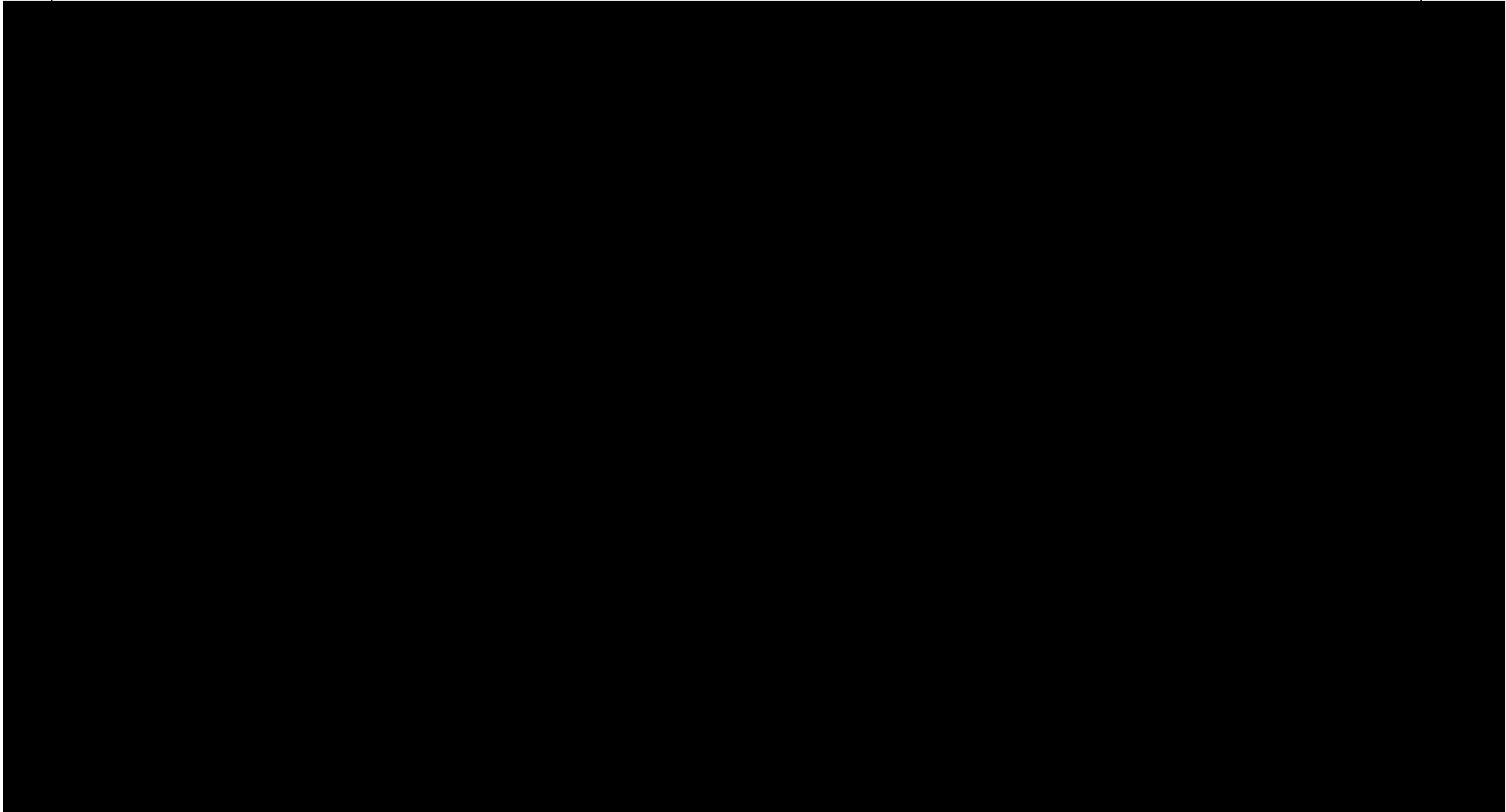


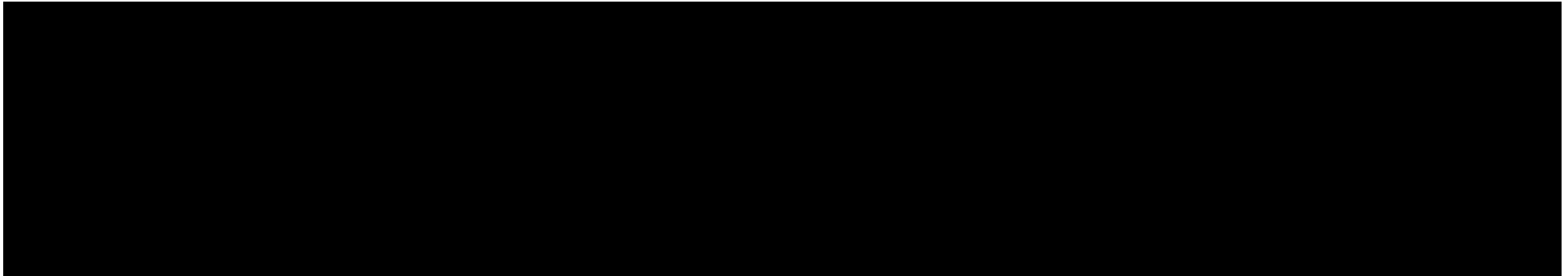
- Standard medical reference texts such as Martindale [redacted] and the British National Formulary ([BNF Estradiol 2024](#)).

The presentation of the ADRs has been aligned with the latest EU QRD and MedDRA requirements. Where necessary, the System Organ Class (SOC) definitions have been updated. The frequencies cited are based on a cumulative review of frequency of events within the global safety database (including both clinical trial as well as postmarketing data).

Adverse effects have been ranked under headings of frequency using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$; $\leq 1/10$); uncommon ($\geq 1/1,000$; $\leq 1/100$); rare ($\geq 1/10,000$; $\leq 1/1,000$); very rare ($<1/10,000$); frequency not known (cannot be estimated from the available data).

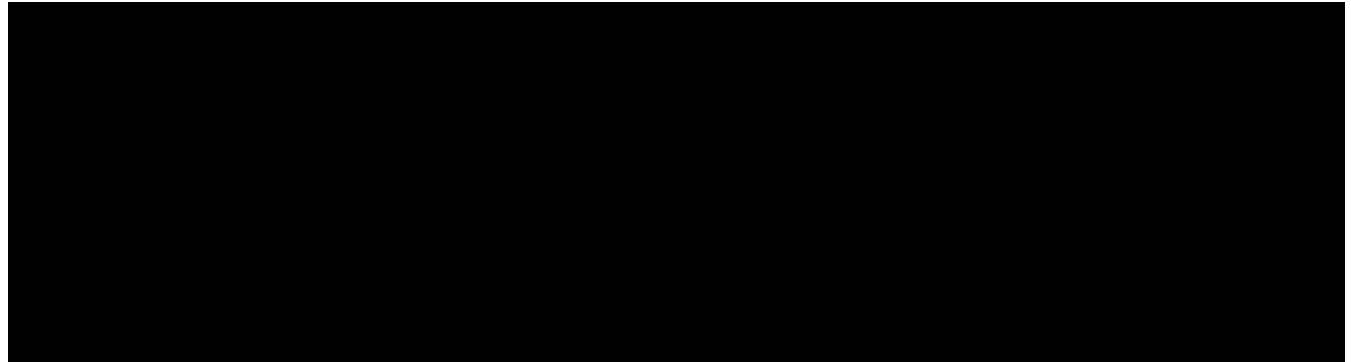
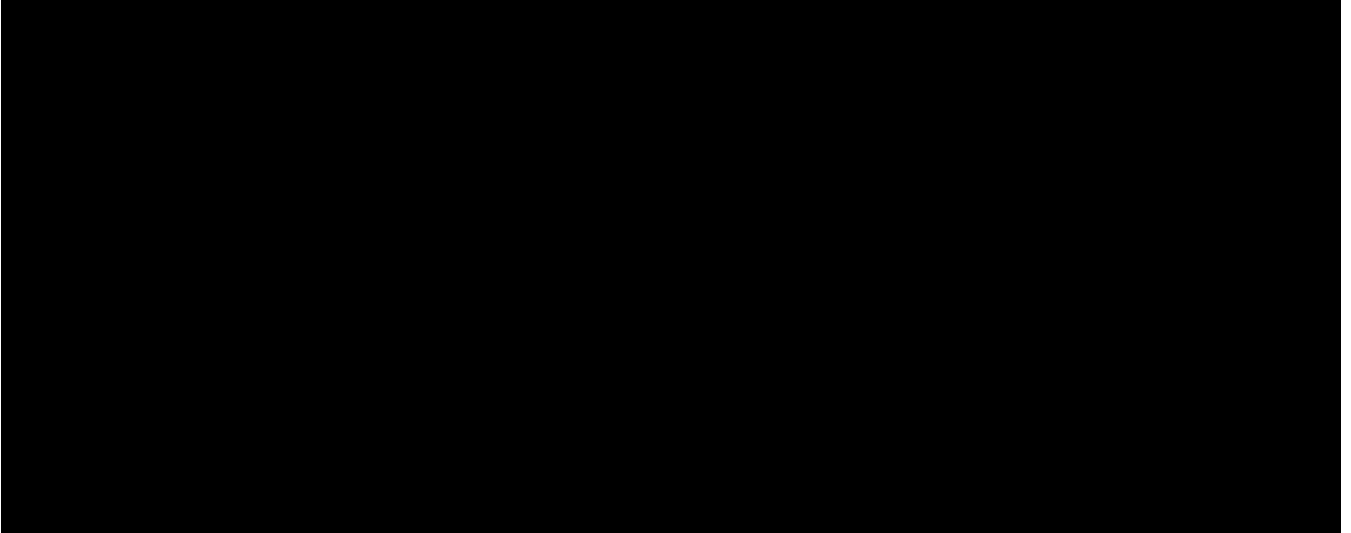
Section 4.8 Undesirable effects – updated sections



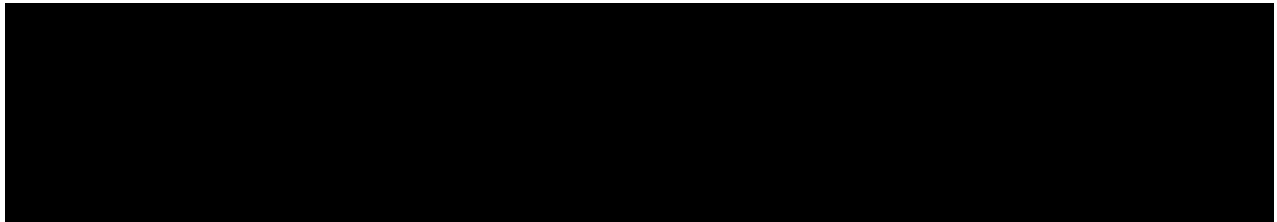


2.5.5.6 FURTHER COMMENTARY ON UPDATES TO SAFETY STATEMENTS

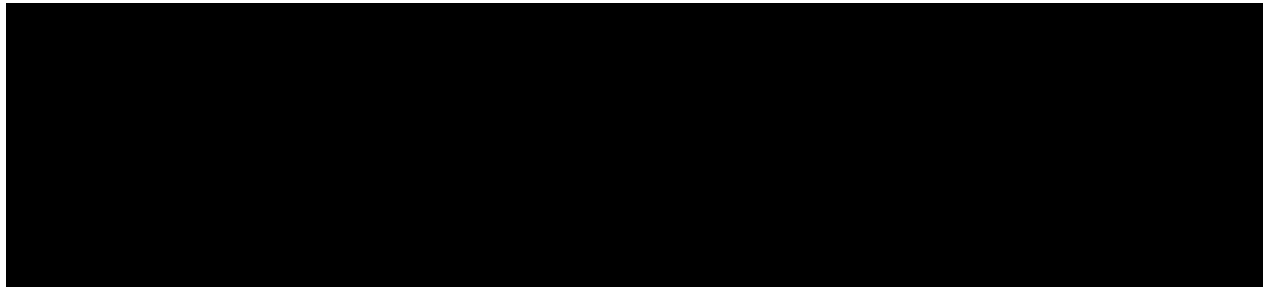
1. Addition of estradiol transfer risk to children



2. Addition of the AE Menorrhagia to table in section 4.8



3. Ethanol Flammability addition



4. Hormone Replacement Therapy Core alignment

Based on the assessment of PSURs of authorised medicines containing estradiol / norgestrel acetate (PSUSA procedure number: [REDACTED] (EU PRAC 2022)), the EMA PRAC has reviewed the benefit-risk balance and issued the following recommendation(s) and conclusions:

- *Based on the review of the data on safety and efficacy, the benefit-risk balance of estradiol/norgestrel acetate-containing products in the approved indication(s) remains unchanged.*
- *The product information should be updated to include exacerbation of symptoms of hereditary and acquired angioedema as a warning, as well as to add a warning on the drug-drug interaction with glecaprevir/pibrentasvir in patients with hepatitis C. Therefore, the current terms of the marketing authorisations should be varied.*

The PRAC has also considered that the warning on exacerbation of symptoms of hereditary and acquired angioedema and the warning relating to the drug-drug interaction with glecaprevir/pibrentasvir is also relevant for estradiol-containing products as a single agent or in fixed-dose combinations. Hereditary and acquired angioedema are added to the conditions for which the patients should take special care while taking Estrogel. Therefore, a recommendation to stop taking Estrogel in case of swollen face, tongue and/or throat and/or difficulty swallowing or hives (together with difficulty breathing which are suggestive of an angioedema) has been added to the PIL.

Furthermore, as regards HRT it has been observed that medicines for Hepatitis C virus (HCV) (such as combination regimen ombitasvir / paritaprevir / ritonavir with or without dasabuvir, as well as a regimen with glecaprevir / pibrentasvir) may cause increases in liver function blood test results (increase in ALT Alanine aminotransferase liver enzyme) in women using Combined Hormonal Contraceptives (CHCs) containing ethinylestradiol. High levels of blood ALT might be considered a sign of a liver injury or disease.

The CMDh has agreed an update of its Core SmPC and PIL (and annexes) for Hormone Replacement Therapy (HRT) products. The Core SmPC/PIL (and annexes) have been updated in line with the conclusions of the PSUSA ([Core PIL for HRT 2023](#), [Core SmPC for HRT 2023](#)).

The observations reported above about HRT-related angioedema and medicines for HCV should be reflected in both the SmPC and the PIL of Estrogel.

It is important to highlight that Estrogel contains estradiol, not ethinylestradiol, and it is not known whether an increase in ALT liver enzyme can occur when using Estrogel with this HCV combination regimen.

A potential interaction with lamotrigine has been added as per EU Core SmPC guidance in Section 4.5 ([Core SmPC for HRT 2023](#)). After absorption, lamotrigine is converted to an inactive substance by several enzymes, including the enzyme UGT1A4. Estradiol can increase the expression of this enzyme and may cause a decrease in lamotrigine blood levels when using estradiol or other oestrogens [REDACTED]

5. Supplementary Information core SmPC HRT vs Estrogel

Throughout the core safety information (CSI) from the CCDS, there is some further wording in relation to the core SmPC for HRT (CMDh) statements and relevance to the Besins Healthcare Estrogel product.

With transdermal administration, the first-pass effect in the liver is avoided [REDACTED] thus, transdermally-applied oestrogens might be less affected than oral hormones by enzyme inducers.

It is essential to include warnings and statements so that patients have the most up to date safety information from the core SmPC for HRT. However, it is also important to highlight the lower risk for these warnings with transdermal applications.

Please see proposed product information text in [Module 1.3.1](#).

2.5.6 BENEFITS AND RISK CONCLUSIONS

The safety aspects of the product information for Estrogel have been comprehensively reviewed and updated to reflect the latest available safety information, to assure that the drug product can be used safely for the approved indications.

Each section of the physicians' and patients' information has been reviewed against relevant EU and, other regional agency guidance, as well as, and internal databases to assure that appropriate safety statements are updated, amended or added.

Taking the proposed changes into account, the previously established benefit-risk for Estrogel remains favourable.

In conclusion, the proposed updates to the PI do not impact the core risk management strategy of Estrogel. The MA Holder will continue to monitor all reports on all the above through routine pharmacovigilance activities.

