Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Estradiol 1mg Film-coated Tablets
Estradiol 2mg Film-coated Tablets

(estradiol hemihydrate)

UK Licence No: PL 00037/0683-0684

Abbott Laboratories Limited.

LAY SUMMARY
Estradiol 1 mg Film-coated Tablets
Estradiol 2 mg Film-coated Tablets

(estradiol hemihydrate)

This is a summary of the Public Assessment Report (PAR) for Estradiol 1 mg Film-coated Tablets (PL 00037/0683) and Estradiol 2 mg Film-coated Tablets (PL 00037/0684). It explains how Estradiol 1 mg and 2 mg Film-coated Tablets were assessed and their authorisations recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Estradiol 1 mg and 2 mg Film-coated Tablets.

For practical information about using Estradiol 1 mg and 2 mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The medicinal products may be collectively referred, to as 'Estradiol Tablets' throughout the remainder of this PAR.

What are Estradiol Tablets and what are they used for?

This medicine is the same as Zumenon 1 mg Film-coated Tablets (PL 46302/0053; Mylan Products Limited) and Zumenon 2 mg Film-coated Tablets (PL 46302/0054; Mylan Products Limited), which is already authorised. The company (Mylan Products Limited) that makes Zumenon 1 mg Film-coated Tablets (PL 46302/0053) and Zumenon 2 mg Film-coated Tablets (PL 46302/0054) has agreed that its scientific data can be used as a basis for the grant of an identical licence for Estradiol Tablets. Zumenon 1 mg Film-coated Tablets (PL 46302/0053) and Zumenon 2 mg Film-coated Tablets (PL 46302/0054) may be collectively referred to as Zumenon Tablets throughout this lay summary. Estradiol Tablets are a Hormone Replacement Therapy (HRT) and are used for the relief of symptoms occurring after menopause. Symptoms include hot face, neck and chest ("hot flushes"). Estradiol Tablets alleviates these symptoms after menopause. The patient will only be prescribed Estradiol if the symptoms seriously hinder daily life.

Estradiol 2mg Film-coated Tablets may additionally be prescribed if the patient is at additional risk of developing osteoporosis. After the menopause some women may develop fragile bones (osteoporosis). The patient should discuss all available options with the doctor. If the patient is at an increased risk of fractures due to osteoporosis and other medicines are not suitable for them, Estradiol 2mg Film-coated Tablets can be given to prevent osteoporosis after menopause.

How do Estradiol Tablets work?

The active ingredient in Estradiol Tablets is estradiol (as hemihydrate). Estradiol Tablets contains the female hormone estrogen. Estradiol is used in postmenopausal women with at least 6 months since the last natural period and women switching from standard (cyclic or sequential) HRT on the advice of the doctor. During the menopause, the amount of the hormone, estrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Estradiol Tablets alleviates these symptoms after menopause. The patient will only be prescribed Estradiol if the symptoms seriously hinder daily life.

How are Estradiol Tablets used?

The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

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

Dose

The patient should take one tablet every day, without a break between packs. The tablet should be swallowed with water, with or without food. In women with a uterus, a progestagen should normally be

added to Estradiol Tablets for 12 - 14 days of each month. If the patient is having regular periods, Estradiol Tablets should be taken on day one of bleeding. If the patient is not having regular periods and is not taking any other HRT preparations, or switching from a combined continuous HRT product, Estradiol Tablets can be taken on any convenient day.

If the patient is currently using a 'cyclic' or 'sequential' HRT preparation (which involves taking an estrogen tablet or patch for part of the month, followed by both estrogen and progestagen tablet or patch for up to 14 days) taking Estradiol 2mg Film-coated Tablets must be taken the day after the pack is finished, i.e. at the end of the progestagen phase. The doctor will aim to prescribe the lowest dose to treat the symptoms for as short as necessary. Speak to the doctor if this dose is too strong or not strong enough. You may experience some irregular bleeding or light bleeding (spotting) during your first few months of taking Estradiol 2mg Film-coated Tablets. If the bleeding is troublesome or continues beyond the first few months of treatment the patient should discuss this with the doctor.

This medicine can only be obtained with a prescription.

For further information on how Estradiol Tablets are used, refer to the package leaflets and Summaries of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Estradiol Tablets have been shown in studies?
Estradiol Tablets are considered to be identical to previously authorised Zumenon Tablets (PL 46302/0053-0054; Mylan Products Limited) with the same benefits and risks. No new studies have been provided for Estradiol Tablets, but reference is made to the studies for Zumenon Tablets (PL 46302/0053-0054; Mylan Products Limited).

What are the possible side effects from Estradiol Tablets?
Like all medicines, Estradiol can cause side effects, although not everybody gets them. The following diseases are reported more often in women using HRT compared to women not using HRT:

- Breast cancer
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer)
- ovarian cancer
- blood clots in the veins of the legs or lungs (venous thromboembolism)
- heart disease
- stroke
- probable memory loss if HRT is started over the age of 65

The following serious side effects may occur during treatment with Estradiol:

- swelling of the skin around the face and neck. This may cause difficulty breathing.
- heart attack
- heavy, irregular or painful bleeds

The most common side effects with Estradiol Tablets are (in less than 1 in 10, but more than 1 in 100 patients treated):

- Headache
- Feeling sick
- Leg cramps
- Abdominal pain
- Pelvic pain
- Unscheduled bleeding or spotting
- Wind (flatulence)
- Feeling weak (asthenia)
- Weight changes
- Rash or itching

For a full list of all the side effects reported with Estradiol Tablets see section 2 and 4 of the package leaflets, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflets.

Why are Estradiol Tablets approved?
The MHRA decided that the benefits of Estradiol Tablets are greater than the risks and recommended that it was approved for use.

What measures are being taken to ensure the safe and effective use of Estradiol Tablets**?**
A Risk Management Plan has been developed to ensure that Estradiol Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Estradiol Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Estradiol Tablets
A Marketing Authorisation was granted in the UK on 28 December 2018.

The full PAR for Estradiol Tablets follows this summary.

For more information about treatment with Estradiol Tablets read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2019.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted the Marketing Authorisation Holder; Abbott Laboratories Limited Marketing Authorisations for the medicinal products Estradiol 1 mg Film-coated Tablets (PL 0037/0683) and Estradiol 2 mg Film-coated Tablets (PL 0037/0684) on 28 December 2018. These products are available as prescription only medicines (POM) indicated for:

- Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women at least 6 months since last menses. Older people. The experience treating women older than 65 years is limited.
- 2mg strength is also indicated for 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.

These applications were submitted as simple abridged (informed consent) applications according to Article 10c of Directive 2001/83/EC, as amended. These applications cross-refer to the reference products Zumenon 1 mg Film-coated Tablets and Zumenon 2mg Film-coated Tablets. Zumenon 1 mg Film-coated Tablets were originally authorised on 01 August 1996 and Zumenon 2 mg Film-coated Tablets were originally authorised on 21 April 1992, both to the Marketing Authorisation Holder; Abbott Healthcare Products Limited. Subsequent change of ownership procedures followed, firstly to the Marketing Authorisation Holder; Mylan UK Healthcare Limited (PL 43900/0056-0057) on 26 March 2015 and then to the current Marketing Authorisation Holder; Mylan Products Limited (PL 46302/0052-0053) on 26 August 2016.

Estradiol is an estrogen only continuous HRT for women with or without a uterus. For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms.

Combined therapy with progestagens is also recommended in hysterectomised women with a history of endometriosis as cancer development in extra-uterine endometriotic implants in women on estrogen-only therapy has been reported (see section 4.4 Special warnings and precautions). Absorption of estradiol is dependent on the particle size: micronized estradiol is rapidly absorbed from the gastrointestinal tract with arithmetic mean Tmax values at steady-state of 3.9 hours. Estrogens can be found either unbound or bound. About 98- 99% of the estradiol dose binds to plasma proteins, from which about 30-52% to albumin and about 46-69% to the sex hormonebindingglobulin (SHBG). Following oral administration, estradiol is extensively metabolised. The major unconjugated and conjugated metabolites are estrone and estrone sulphate. These metabolites can contribute to the estrogen activity, either directly or after conversion to estradiol. Estrone sulphate may undergo enterohepatic circulation. In urine, the major compounds are the glucuronides of estrone and estradiol. The elimination half- life of estradiol and its main metabolites is between 10-16 h.
Estrogens are secreted in the milk of nursing mothers. The mean estradiol exposure at steady-state after oral daily dosing of 2 mg micronized estradiol is approximately 2-fold greater than that after daily dosing of 1 mg micronized estradiol. Based on the elimination half-life of the micronized estradiol, it can be estimated that estradiol concentrations reach steady-state approximately within one week following oral daily administration.

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to the data for the previously granted reference product.

II QUALITY ASPECTS

II.1 Introduction

These are abridged applications for Estradiol 1 mg Film-coated Tablets (PL 0037/0683) and Estradiol 2 mg Film-coated Tablets (PL 0037/0684) submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications cross-refer to the reference products Zumenon 1 mg Film-coated Tablets (PL 46302/0053) and Zumenon 2 mg Film-coated Tablets (PL 46302/0054) which, were originally authorised on 01 August 1996 and Zumenon 2 mg Film-coated Tablets were originally authorised on 21 April 1992, both to the Marketing Authorisation Holder; Abbott Healthcare Products Limited. Subsequent change of ownership procedures followed, firstly to the Marketing Authorisation Holder; Mylan UK Healthcare Limited (PL 43900/0056-0057) on 26 March 2015 and then to the current Marketing Authorisation Holder; Mylan Products Limited (PL 46302/0052-0053) on 26 August 2016.

II.2. Drug Substance

Drug substance specifications

The proposed drug substances specifications are consistent with the details registered for the cross-reference products.

II.3. Medicinal Product Name

The proposed product name for these applications are Estradiol 1 mg Film-coated Tablets and Estradiol 2 mg Film-coated Tablets. Diomed Haemorrhoids Cutaneous Spray. The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

Estradiol Tablets are available in blister packs of polyvinyl chloride (PVC) film with an aluminium foil covering. Each carton contains 84 tablets (blister strips of 28 tablets each).

The proposed shelf life of the product is 3 years with no special storage conditions.

The proposed packaging, shelf life and storage conditions are consistent with the details registered for the reference product.

Legal status

Prescription Only Medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company

Abbott Laboratories Limited
Abbott House
Vanwall Business Park Vanwall Road Maidenhead
Berkshire SL6 4XE United Kingdom

Manufacturers

The proposed manufacturing sites are consistent with those registered for the reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative compositions

The proposed product composition is consistent with the details registered for the reference products.

Manufacturing process

The proposed manufacturing processes are consistent with the details registered for the reference products and the maximum batch size is stated.

Finished product/shelf life specifications

The proposed finished product specification is in line with the details registered for the reference products.

TSE Compliance
With the exception of lactose monohydrate none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

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

Bioequivalence
No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formula utilising the same processes as the reference products, The applications cross-refer to the reference products Zumenon 1 mg Film-coated Tablets and Zumenon 2 mg Film-coated Tablets (PL 46302/0053-0054; Mylan Products Limited).

Expert Report
The applicant cross-refers to the data for Zumenon 1 mg Film-coated Tablets and Zumenon 2 mg Film-coated Tablets (PL 46302/0053-0054; Mylan Products Limited), to which this applications iare claimed to be identical. This is acceptable.

Product Name and Appearance
See Section II.3 'Medicinal Product; Name' for details of the proposed product name. The appearance of the products are identical to that of the reference products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with these applications is acceptable. The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

Introduction
As these applications are submitted under Article 10c of Directive 2001/83/EC, as amended, (as an informed consent application) no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of Marketing Authorisations is recommended.

IV CLINICAL ASPECTS

Introduction
As these applications are submitted under Article 10c of Directive 2001/83/EC, as amended, (as an informed consent application) no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Table 5. Summary of Important Safety Concerns	
Type	**Safety Concerns**
Important identified risks	◦ Arterial thromboembolic disease ◦ Venous thromboembolic disease ◦ Breast cancer ◦ Ovarian cancer ◦ Endometrial cancer ◦ Hepatic disorders ◦ Gallbladder disorders
Important potential risks	◦ None
Missing information	◦ None

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation

As the PILs for Estradiol Tablets (PL 00037/0683-0684) are aligned with the European Core PIL for HRT issued by CMDh, it can therefore be used as a justification for not conducting a User Test for Estradiol Tablets (PL 00037/0683/0684).

A core Package Leaflet for Hormonal Replacement Therapy (HRT) Products based on a core SmPC HRT has been drafted by CMDh (doc. Ref.: CMDh/240/2011, Rev 4) and revised in February 2017. The Package Information Leaflets (PILs) for Estradiol Tablets (PL 00037/0683/0684) have been written so that they are aligned to the CMDh HRT core Package Leaflet and therefore no User Testing has been carried out.

This bridging report follows the recommendations for bridging provided by CMDh in their guidance issued in October 2007. They indicate that although all patient information leaflets (PILs) for medicines must reflect the results of consultation with target patient groups (user testing) not every leaflet needs be the subject of a separate user test. PILs may be able to rely on testing applied to leaflets for similar products, provided that the key messages for safe use have been adequately addressed. In this case the core Package Leaflet for Hormonal Replacement Therapy (HRT) Products provided by CMDh can be considered the reference or “parent” PIL.

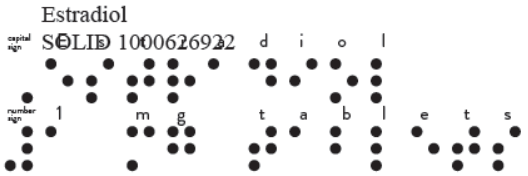
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the reference product. Extensive clinical experience with estradiol (as hemihydrate) is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be similar to the referenced product and positive.

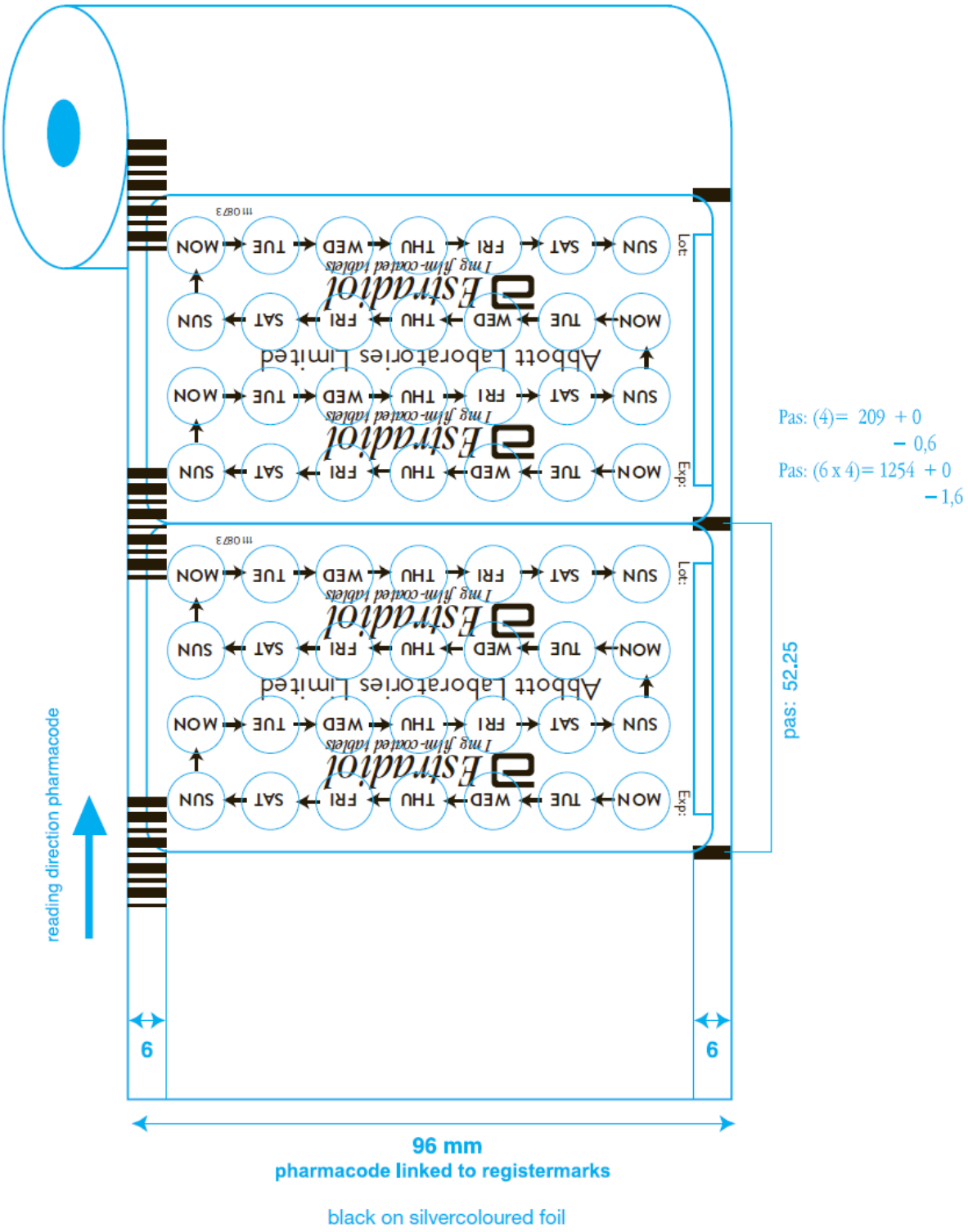
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The SmPC and PIL are consistent with the details registered for the reference product.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Estradiol 1 mg and 2 mg Film-coated Tablets is presented below:

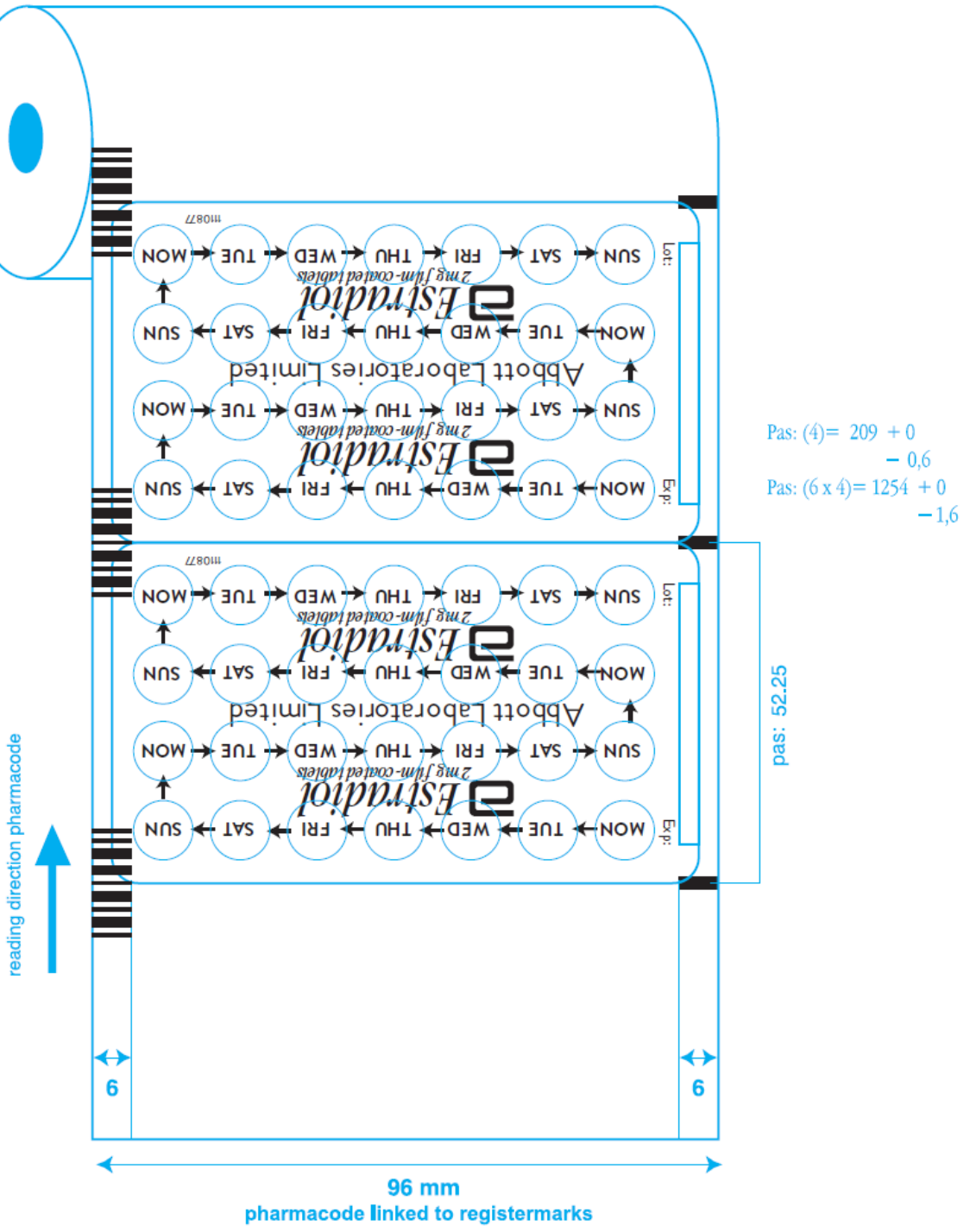


Recto: outside of foil



Estradiol
SOLID 1000626923 d i o l v2.0
2 m g t a b l e t s

Recto: outside of foil



Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)