Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Diethylstilbestrol 1mg film-coated tablets

(Diethylstilbestrol)

UK Licence No: PL 44710/0016

Kinedexe UK Limited

LAY SUMMARY
Diethylstilbestrol 1mg film-coated tablets
(Diethylstilbestrol)

This is a summary of the Public Assessment Report (PAR) for Diethylstilbestrol 1mg film-coated tablets (PL 44710/0016). It explains how Diethylstilbestrol 1mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Diethylstilbestrol 1mg film-coated tablets.

This product will be referred to as Diethylstilbestrol tablets throughout the remainder of this lay summary (PAR) for ease of reading.

For practical information about using Diethylstilbestrol tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Diethylstilbestrol tablets and what are they used for?
Diethylstilbestrol tablets are a medicine with a 'well established use'. This means that the medicinal use of the active substance, diethylstilbestrol, is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Diethylstilbestrol Tablets are used specifically for men with prostate cancer who have not responded to other drug or surgery forms of castration and for whom alternative treatments are not suitable.

How do Diethylstilbestrol tablets work?
Diethylstilbestrol 1mg film-coated tablets contain the active ingredient diethylstilbestrol, which is a synthetic non-steroidal oestrogen hormone. This medicine inhibits the hypothalamic-pituitary-gonadal axis, thereby blocking the testicular synthesis of testosterone, lowering plasma testosterone, and inducing a chemical castration.

How are Diethylstilbestrol tablets used?
Diethylstilbestrol tablets are taken by mouth. The whole tablet is swallowed with a drink of water.

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

The recommended dose in adults and elderly with prostate cancer is one to three 1 mg tablets per day. In some patients, a doctor may consider prescribing a blood thinning agent such as low dose aspirin to prevent clots forming. Before taking diethylstilbestrol a doctor may offer patients breast bud radiation to minimise some of the side effects associated with diethylstilbestrol.

Diethylstilbestrol tablets are not recommended for use in children.

This medicine can only be obtained with a prescription.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

What benefits of Diethylstilbestrol tablets have been shown in studies?
As diethylstilbestrol is a well-known substance, and its use in the licenced indication is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of diethylstilbestrol in the licensed indication.

In addition, the company (Kinedexe UK Limited) undertook a bioequivalence study to bridge their product to the information found in the bibliographic sources relating to the currently approved diethylstilbestrol -containing product. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Diethylstilbestrol tablets?
Like all medicines, Diethylstilbestrol tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Diethylstilbestrol tablets, see section 4 of the package leaflet available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

Why were Diethylstilbestrol tablets approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of Diethylstilbestrol tablets outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of Diethylstilbestrol tablets?
A risk management plan (RMP) has been developed to ensure that Diethylstilbestrol tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Diethylstilbestrol 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 Diethylstilbestrol tablets
A Marketing Authorisation for Diethylstilbestrol tablets was granted in the UK on 19 June 2017.

The full PAR for Diethylstilbestrol tablets follows this summary.

This summary was last updated in August 2017.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Kinedexe UK Limited a Marketing Authorisation for the medicinal product Diethylstilbestrol 1mg film-coated tablets (PL 44710/0016) on 19 June 2017. The product is a prescription only medicine (POM), indicated for the treatment of castration-resistant carcinoma of the prostate in patients for whom alternative forms of therapy are not suitable.

The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Like other oestrogens action of diethylstilbestrol is intracellular. It is bound to a receptor protein in the cytoplasm and translocated to the nucleus where binding to chromatin occurs. Specific Messenger Ribonucleic Acid (MRNA) and specific proteins are then synthesised.

Bibliographic data on diethylstilbestrol have been submitted to support this application. No new non-clinical studies were conducted for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

In addition to the submission of published non-clinical and clinical references the applicant has also performed a bioequivalence study to bridge their product to the information found in the bibliographic sources relating to a currently approved diethylstilbestrol containing product, Diethylstilbestrol 1mg film-coated tablets, (Teva U.K. Limited). The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.

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

II QUALITY ASPECTS

II.1 Introduction

The finished product is presented as a film-coated tablets and each tablet contains 1 mg of diethylstilbestrol as active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, magnesium stearate (E572), maize starch, ethanol and opadry II pink 85F24252 (polyvinyl alcohol, titanium dioxide (E171), polyethylene glycol/ macrogol, talc, erythrosine aluminium lake (E127), sunset yellow FCF aluminium lake (E110) and indigo carmine aluminium lake (E132)).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of opadry II pink 85F24252 which is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate and maize starch used in the tablets are of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

The finished product is packed into polyvinyl chloride (PVC)/ polyvinylidenechloride (PVdC) or Alu/Alu blister strips in packs of 10, 28, 30, 56, 60 and 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

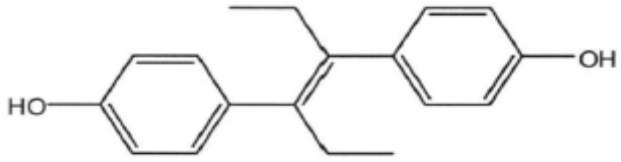
II.2 Drug Substances

Diethylstilbestrol

INN: **Diethylstilbestrol**

Chemical name: Phenol 4, 4’-(1,2-diethyl-1,2-ethenediyl)bis-,(E)-a,a’-Diethyl-(E)-4,4’-stilbenediol

Structure:



Molecular formula: $C_{18}H_{20}O_2$

Molecular weight: 268.35 g/mol

Appearance: White or almost white crystalline powder.

Solubility: Practically insoluble in water and soluble in ethanol, chloroform, diethyl ether, acetone, dioxane, ethyl acetate, methyl alcohol, vegetable oils, and aqueous solutions of alkaline hydroxides.

Diethylstilbestrol is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been provided supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, film-coated tablets that are equivalent to the UK generic product Diethylstilbestrol 1 mg tablets (TEVA UK Limited).

Comparative dissolution profile has been provided for the proposed and originator products.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with no special storage conditions.

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

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of diethylstilbestrol 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.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Diethylstilbestrol 1mg film-coated tablets are intended for generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
This is a national application for a Marketing Authorisation for Diethylstilbestrol 1mg film-coated tablets. The legal basis of this application is well-established use according to Article 10a of Directive 2001/83/EC as amended, supported by bibliographic literature.

One bioequivalence study was submitted to support this application. The study was designed to demonstrate that the test product, Diethylstilbestrol 1mg film-coated tablets was bioequivalent to the currently approved product, Diethylstilbestrol 1mg film-coated tablets, (Teva U.K. Limited).

With the exception of the bioequivalence study, no new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of diethylstilbestrol.

The Applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
An open-label, randomised, balanced, two-treatment, three-period, three-sequence, partial reference replicated, single-dose, crossover, oral bioequivalence study of Diethylstilbestrol 1 mg Tablets with Diethylstilbestrol 1 mg Tablets (Teva U.K. Limited) in healthy, adult, male, human subjects under fasting conditions.

Subjects were administered a single oral dose of study drugs with 240 mL of water. Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between the treatment phases was 10 days.

Results

The pharmacokinetic results are presented below:

PK parameter	Geometric Least square Mean (Test)	Geometric Least Square Mean (Reference)	Ratio (T/R)	90% CI [Lower, Upper]
C_{max} (pg/mL)	3672.44	3623.84	101.34	90.99 - 112.87
AUC_{0-t} (pg.hr/mL)	9741.84	9912.34	98.28	94.73 - 101.96

Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC_{0-t} and C_{max} values for diethylstilbestrol lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). However, the reference product is considered to be a generic medicine and the results from this study are stated by the Applicant to be supportive only (comparability between the test and reference).

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of diethylstilbestrol is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application. Safety is adequately reviewed in the clinical overview. The safety profiles of diethylstilbestrol are well-known.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Diethylstilbestrol 1mg film-coated tablets.

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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk – • Vaginal carcinoma in female offspring if used during pregnancy	Details of this safety concern are included in sections 4.3, 4.4, 4.6 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Acceleration of the growth of oestrogen-dependent neoplasms; especially of the genital tract, pre-menopausal carcinoma of the breast, endometrial hyperplasia and uterine fibromyomata (fibroids)	Details of this safety concern are included in sections 4.3 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Exacerbations of porphyria	Details of this safety concern are included in section 4.3 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Hypertension	Details of this safety concern are included in sections 4.3, 4.4 and 4.5 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Thrombo-embolism	Details of this safety concern are included in sections 4.3, 4.4 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – Risk in patients with hepatic impairment	Details of this safety concern are included in sections 4.3, 4.4 and 4.8 of the SmPC and appropriate advice for patients	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	is provided in the PIL	
Important identified risk – • Carcinogenicity	Details of this safety concern are included in sections 4.4 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Metabolic disturbance e.g. lowered glucose tolerance, sodium and water retention	Details of this safety concern are included in sections 4.4 and 4.8 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk Risks in patients with renal impairment	Details of this safety concern are included in section 4.4 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Risk in patients with cardiovascular or cerebrovascular disease	Details of this safety concern are included in sections 4.3and 4.4 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Increase in thyroid hormone binding and circulating total thyroid hormone	Details of this safety concern are included in section 4.4 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – • Drug-drug interaction with antihypersensitives and diuretics	Details of this safety concern are included in section 4.5 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important identified risk – Teratogenicity	Details of this safety concern are included in section 4.6 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Important potential risk • Malignancy in the third generation	Details of this safety concern are included in section 5.3 of the SmPC and appropriate advice for patients is provided in the PIL	None proposed
Missing information – • None	-	None proposed

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

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application.

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 patient information leaflet (PIL) was English.

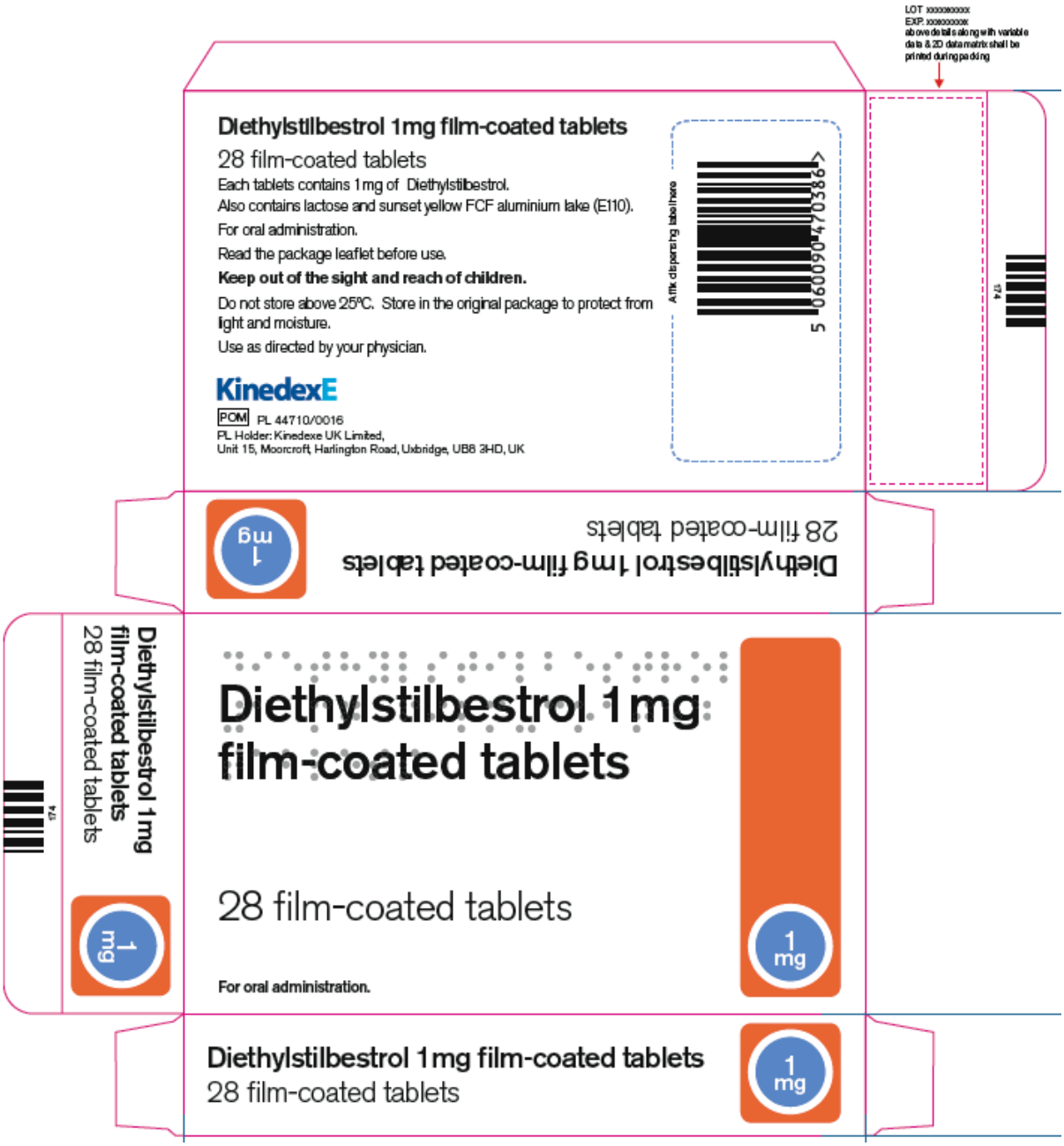
The package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

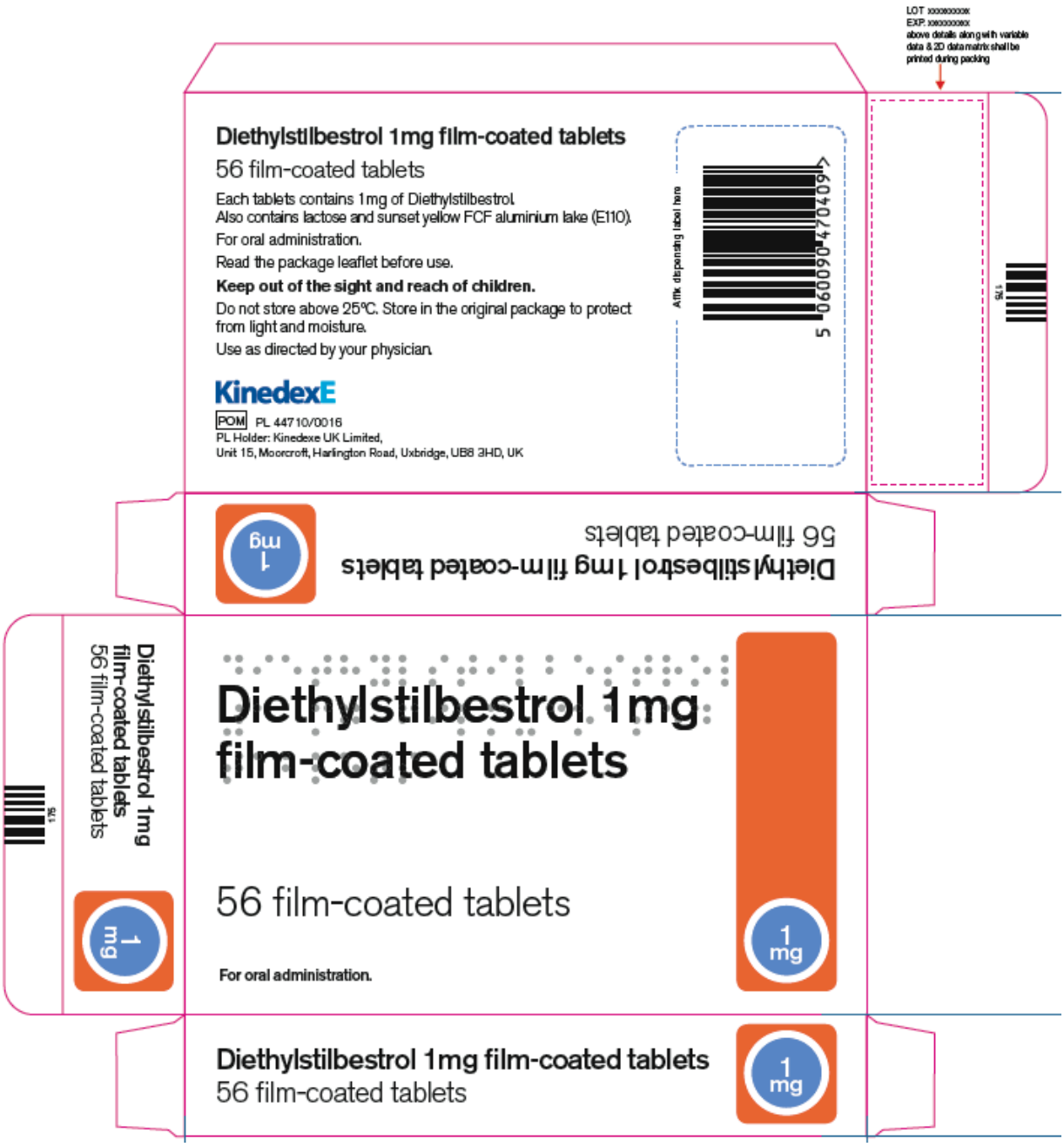
VI Overall conclusion, benefit/risk assessment and recommendation

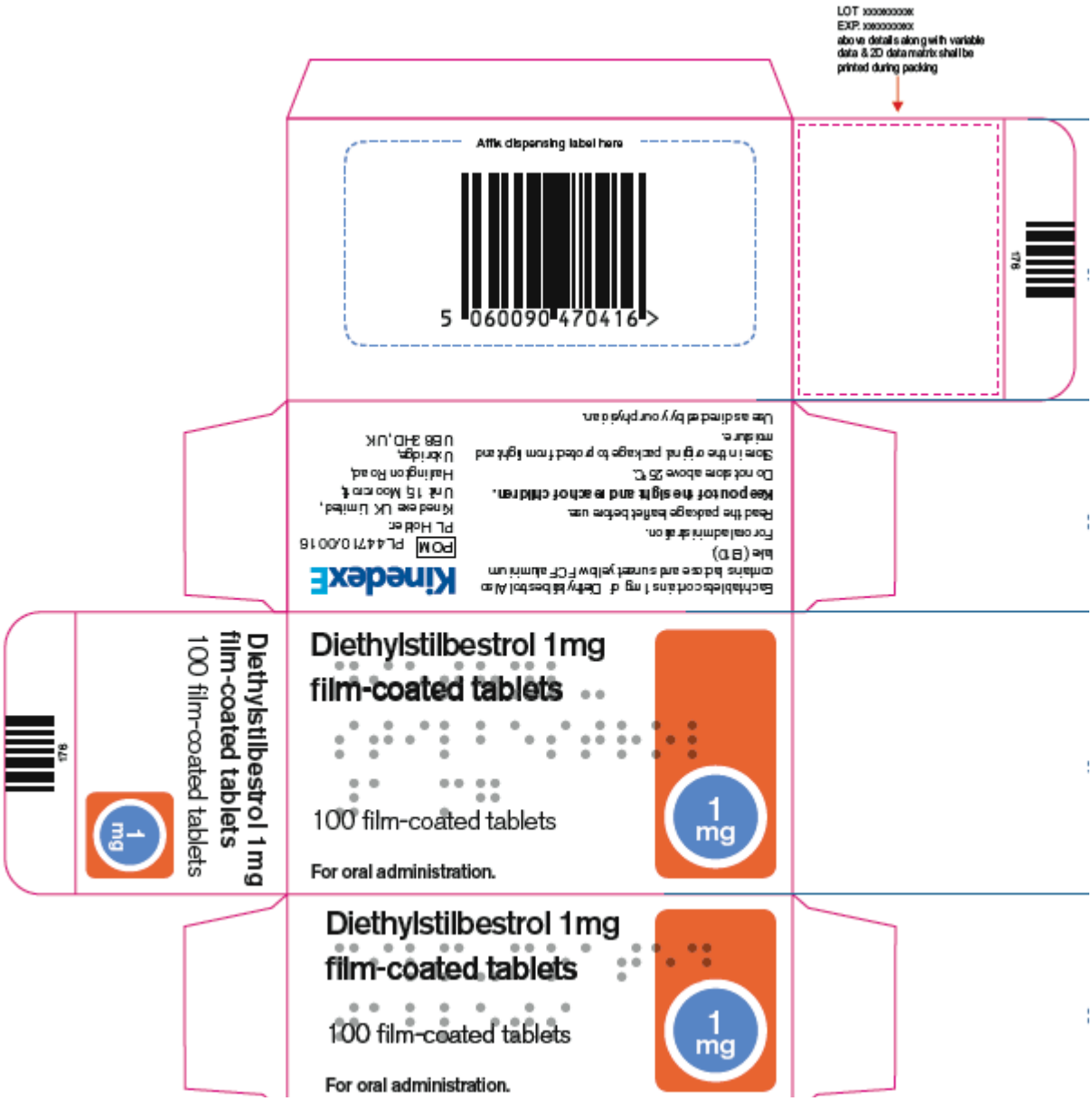
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with diethylstilbestrol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.

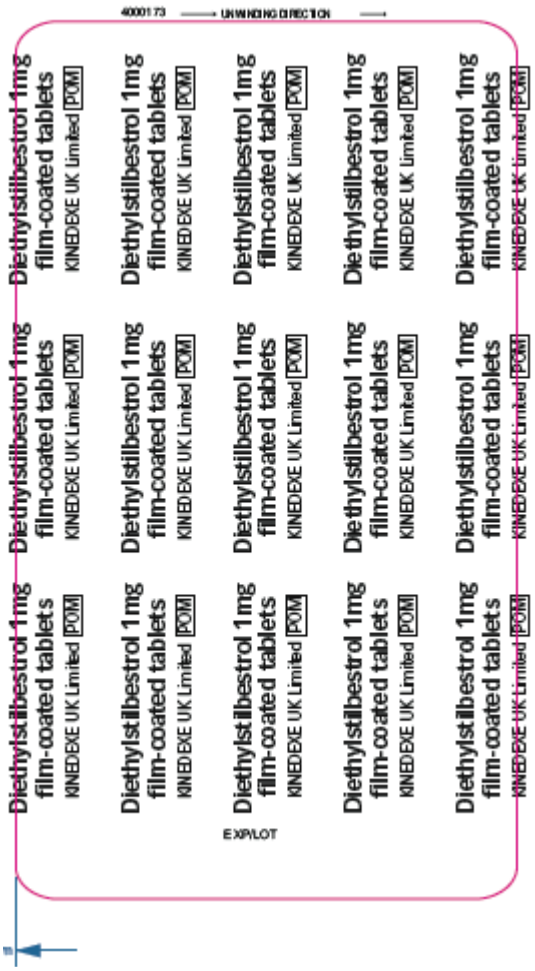
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the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

The approved labelling for Diethylstilbestrol 1mg film-coated tablets is presented below:




LOT xxxxxxxxx
EXP xx/xx/xxxx
above details along with variable data & 2D data matrix shall be printed during packing
Diethylstilbestrol 1mg film-coated tablets
56 film-coated tablets
Each tablets contains 1mg of Diethylstilbestrol.
Also contains lactose and sunset yellow FCF aluminium lake (E110).
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25ºC. Store in the original package to protect from light and moisture.
Use as directed by your physician.
KinedexE
POM PL 44710/0016
PL Holder: Kinedexe UK Limited,
Unit 15, Moorcroft, Harlington Road, Uxbridge, UB8 3HD, UK
A/Nk depending label here
5 060090 470409
SLS
1 mg
Diethylstilbestrol 1mg film-coated tablets
56 film-coated tablets
Diethylstilbestrol 1mg film-coated tablets
56 film-coated tablets
1 mg
Diethylstilbestrol 1mg film-coated tablets
56 film-coated tablets
For oral administration.
1 mg
Diethylstilbestrol 1mg film-coated tablets
56 film-coated tablets
1 mg


LOT xxxxxxxxx
EXP xxxxxxxxx
above details along with variable data & 2D data matrix shall be printed during packing
Affix dispensing label here
5 060090 470416 >
Each tablet contains 1 mg of Diethylstilbestrol Also contains lactose and sunset yellow FCF aluminium lake (E110)
For oral administration.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not store above 25°C.
Store in the original package to protect from light and moisture.
Use as directed by your physician.
Kinedex
POM PL 44710/0016
PL Holder:
Kinedex UK Limited,
Unit 15 Moorcroft,
Hailington Road,
Uxridge,
UB8 3HD, UK
Diethylstilbestrol 1mg film-coated tablets
100 film-coated tablets
1 mg
Diethylstilbestrol 1mg film-coated tablets
100 film-coated tablets
For oral administration.
1 mg
Diethylstilbestrol 1mg film-coated tablets
100 film-coated tablets
For oral administration.
1 mg


40001173
UNWINDING DIRECTION
Diethylstilbestrol 1mg film-coated tablets
KINEDEXE UK Limited POM
EXP/LOT

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)