Public Assessment Report

UKPAR

Teragezza 2000/35 microgram Film-coated Tablets
(cyproterone acetate and ethinylestradiol)

UK Licence No: PL 20117/0106

Morningside Healthcare Ltd
LAY SUMMARY
Teragezza 2000/35 microgram Film-coated Tablets
(cyproterone acetate and ethinylestradiol)

This is a summary of the Public Assessment Report (PAR) for Teragezza 2000/35 microgram Film-coated Tablets (PL 20117/0106). It explains how Teragezza 2000/35 microgram 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 this product.

For practical information about using Teragezza 2000/35 microgram Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Teragezza 2000/35 microgram Film-coated Tablets and what are they used for?
Teragezza 2000/35 microgram Film-coated Tablets is a ‘generic medicine’. This means that Teragezza 2000/35 microgram Film-coated Tablets are similar to a ‘reference medicine’ already authorised in the UK called Dianette® (Bayer plc; PL 00010/0526).

Teragezza is used to treat skin conditions such as acne, very oily skin and excessive hair growth in women of reproductive age. Due to its contraceptive properties it should only be prescribed if a doctor considers that treatment with a hormonal contraceptive is appropriate. Patients should only take Teragezza if their skin condition has not improved after use of other anti-acne treatments, including topical treatments and antibiotics.

How do Teragezza 2000/35 microgram Film-coated Tablets work?
Teragezza 2000/35 microgram Film-coated Tablets contain the active ingredients: cyproterone acetate, an anti-androgen, and ethinylestradiol, an oestrogen. Androgens are hormones that stimulate hair growth and the grease glands in the skin. Teragezza stops the androgens affecting the skin and reduces the amount of androgens produced and also reduces the free circulating plasma levels of androgens. Teragezza also prevents pregnancy.

How are Teragezza 2000/35 microgram Film-coated Tablets used?
Teragezza 2000/35 microgram Film-coated Tablets are taken by mouth. The whole tablet should be swallowed with water without chewing. This medicinal product can only be obtained on prescription from a doctor.

Teragezza comes in strips of 21 pills, each marked with a day of the week. The pill should be taken everyday at the same time for 21 days. Following completion of the 21 pills in the strip, there will be seven pill-free days until the start of the next strip. Within a few days of taking the last pills, the patient may have a withdrawal bleed like a period which may not have finished when it is time to start the next strip of pills. The next strip of Teragezza should be taken after the seven pill-free days even if the patient is still bleeding.

For further information on how Teragezza 2000/35 microgram Film-coated Tablets are used, refer to the Summary of Product Characteristics or package leaflet available on the MHRA website.

What benefits of Teragezza 2000/35 microgram Film-coated Tablets have been shown in studies?
As Teragezza 2000/35 microgram Film-coated Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to DIANE® 35 microgram tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Teragezza 2000/35 microgram Film-coated Tablets?
Because Teragezza 2000/35 microgram Film-coated Tablets is a generic medicine and is bioequivalent to DIANE® 35 microgram tablets, its benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Teragezza 2000/35 microgram Film-coated Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Teragezza 2000/35 microgram Film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Teragezza 2000/35 microgram Film-coated Tablets have been shown to have comparable quality and to be bioequivalent to DIANE® 35 microgram tablets. Therefore, the MHRA decided that, as for DIANE® 35 microgram tablets, the benefits of Teragezza 2000/35 microgram Film-coated Tablets are greater than its risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Teragezza 2000/35 microgram Film-coated Tablets?
A risk management plan has been developed to ensure that Teragezza 2000/35 microgram Film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Teragezza 2000/35 microgram Film-coated 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 as well.

Other information about Teragezza 2000/35 microgram Film-coated Tablets
A Marketing Authorisation was granted in the UK on 3rd March 2015.

The full PAR for Teragezza 2000/35 microgram Film-coated Tablets follows this summary.

For more information about treatment with Teragezza 2000/35 microgram Film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Morningside Healthcare Ltd a Marketing Authorisation for the medicinal product Teragezza 2000/35 microgram Film-coated Tablets (PL 20117/0106). The product is a prescription-only medicine (POM) indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

For the treatment of acne, Teragezza should only be used after topical therapy or systemic antibiotic treatments have failed. Since Teragezza is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives.

This application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross-referred to Dianette®, which was originally authorised to Schering Health Care Limited (PL 00053/0190) on 11th June 1987. This reference licence underwent a change of ownership procedure to the currently Marketing Authorisation Holder, Bayer plc (PL 00010/0526), on 1st May 2008.

Teragezza blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitary-ovarian systems and by the inhibition of androgen-synthesising enzymes. Although Teragezza also acts as an oral contraceptive, it is not recommended in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent skin conditions described.

A bioequivalence study was submitted to support this application comparing the applicant’s test product Cyproterone acetate 2.0 mg and Ethinylestradiol 0.035 mg tablets (Famy Care Ltd, India) with the reference product DIANE® 35 microgram tablets (Bayer Schering Pharma) in healthy adult female subjects under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP) requirements.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Teragezza 2000/35 microgram Film-coated Tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction

Each tablet contains 2000 micrograms of cyproterone acetate and 35 micrograms of ethinyleradiol, as active ingredients. The excipients present are lactose monohydrate, maize starch, povidone, talc, magnesium stearate and Opadry pink – 03F540049 (hypermellose (E464), talc, macrogol (E1521), titanium dioxide (E171) and red iron oxide (E172)). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry pink – 03F540049 which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for these excipients.

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 used in the tablets is of vegetable origin.

The finished product is packed in an aluminium backed blister consisting of clear, transparent polyvinylchloride (PVC) film coated with polyvinylidene chloride (PVdC) optionally in an aluminium foil pouch containing 21, 63 and 126 Tablets.

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

II.2 Drug Substance

INN: Cyproterone acetate

The chemical name: 6-chloro-3,20-dioxo-1β,2β-dihydro-3'H-cyclopropa-[1,2]pregna-1,4,6-trien-17-yl acetate.

Structural formula:

![Structural formula of Cyproterone acetate](image)

Molecular formula: $C_{24}H_{29}ClO_4$

Molecular mass: 416.9 g/mol

Appearance: white or almost white crystalline powder.

Solubility: Cyproterone acetate is practically insoluble in water, very soluble in methylene chloride, freely soluble in acetone, soluble in methanol and sparingly soluble in anhydrous ethanol.

Cyproterone acetate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, cyproterone acetate, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
Ethinylestradiol
Chemical name: 19-Nor-17α-pregn-13,5 (10)-tren-20-yne-3,17-diol.
Structure:

\[
\begin{align*}
\text{Molecular formula:} & \quad \text{C}_{20}\text{H}_{24}\text{O}_2 \\
\text{Molecular mass:} & \quad 296.4 \text{ g/mol} \\
\text{Appearance:} & \quad \text{White or slightly yellowish white crystalline powder.} \\
\text{Solubility:} & \quad \text{Ethinylestradiol is practically insoluble in water, freely soluble in ethanol and it} \\
& \quad \text{dissolves in dilute alkaline solutions.}
\end{align*}
\]

Ethinylestradiol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ethinylestradiol, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, tablets containing cyproterone acetate and ethinylestradiol that are bioequivalent to Dianette® (Bayer plc).

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity and in-vitro dissolution profiles have 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 and has shown satisfactory results. Process validation data on pilot scale batches have been provided. The applicant has committed to perform further process validation on full scale commercial batches.

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 specifications. 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 finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with a storage condition “Store in the original package in order to protect from light”.
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 cyproterone acetate and ethinylestradiol 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 Teragezza 2000/35 microgram Film-coated Tablets are intended for generic substitution, this 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
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of cyproterone acetate and ethinylestradiol is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided and none are required for this type application.

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 cyproterone acetate and ethinylestradiol.
Based on the data provided, Teragezza 2000/35 microgram Film-coated Tablets can be considered bioequivalent to DIANE® 35 microgram tablets (Bayer Schering Pharma).

IV.2 Pharmacokinetics
In support of this application, the applicant has conducted a single dose bioequivalence study under fasting conditions comparing the test product with the reference product.

This was an open label, single dose, balanced, randomised, two-treatment, two-period, crossover bioequivalence study comparing the pharmacokinetics of the applicant’s test product Cyproterone acetate 2.0 mg and Ethinylestradiol 0.035 mg tablets (Famy Care Ltd., India) versus the reference product, DIANE® 35 microgram tablets (Bayer Schering Pharma) in 34 healthy adult female subjects under fasting conditions.

A single dose of the investigational products was administered orally to each subject. A washout period of one month was maintained between the two periods of the study.

Serial blood sampling at pre-dose and at 00.00, 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 03.00, 03.50, 04.00, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00 & 72.00 hrs post-dose was carried out in each period.

Results

### Statistical Results of Test Product-T versus Reference Product-R for Cyproterone

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Anti Log of Least Square Mean</th>
<th>90% Confidence Interval (T/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/ml)</td>
<td>Test (T) 24.4647</td>
<td>Reference (R) 23.6735</td>
</tr>
<tr>
<td>AUC_{0-72} (ng.hr/ml)</td>
<td>238.6132</td>
<td>227.2880</td>
</tr>
</tbody>
</table>

### Statistical Results of Test Product-T versus Reference Product-R for Ethinylestradiol

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Anti Log of Least Square Mean</th>
<th>90% Confidence Interval (T/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (pg/mL)</td>
<td>Test (T) 126.4157</td>
<td>Reference (R) 113.2692</td>
</tr>
<tr>
<td>AUC_{0-1} (pg.hr/mL)</td>
<td>1466.5716</td>
<td>1445.6403</td>
</tr>
<tr>
<td>AUC_{0-∞} (pg.hr/mL)</td>
<td>1671.9281</td>
<td>1597.3414</td>
</tr>
</tbody>
</table>

Conclusion
The 90% confidence intervals for C_{max} and AUC for both components were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1 / Corr**). Bioequivalence has been shown for the test formulation (Cyproterone acetate 2.0 mg and Ethinylestradiol 0.035 mg tablets) and the reference formulation (DIANE® 35 microgram tablets) under fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.
**IV.6 Risk Management Plan (RMP)**

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 Teragezza 2000/35 microgram Film-coated Tablets.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Venous thromboembolism | Risk of venous thromboembolism is considered to be adequately addressed in the currently proposed SPC and PIL.  
- As per SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with existing or a history of confirmed VTE.  
- Warning in SPC Section 4.4 and PIL Section 4, when first signs of venous thrombosis or blood clots in veins are noticed, Co-Cyprindiol should be discontinued and doctor should be contacted immediately.  
- Listed in SPC Section 4.8, thromboembolism is a rare vascular disorder (seen in less than 1 person per 1000 users). Venous thromboembolic disorder is one of the reported SAEs. | Physician education material and patient education material. |
| Arterial thromboembolism | Risk of ATE is considered to be adequately addressed in the currently proposed SPC and PIL.  
- As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with patients with existing or previous arterial thrombotic or embolic processes.  
- Warning in SPC Section 4 and PIL Section 4, when first signs of venous arterial thrombosis or blood clots in arteries are noticed, Co-Cyprindiol should be discontinued and doctor should be contacted immediately.  
- Listed in SPC Section 4.8, thromboembolism is a rare vascular disorder (seen in less than 1 person per 1000 users). Arterial thromboembolic disorder is one of the reported SAEs. | Physician education material and patient education material. |
<p>| Severe liver impairment or use in patients with severe hepatic disease (or a history of hepatic impairment) | The risk of severe liver impairment or use in patients with severe hepatic disease (or a history of hepatic disease) is considered to be adequately addressed in the currently proposed SPC and PIL. As per SPC | None |</p>
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>disease</td>
<td>Section 4.3 and PIL Section 2. Co-Cyprindiol should not be used in patients with presence or history of severe hepatic disease.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Warning in the SPC Section 4.4 and PIL Sections 2 and 4, Co-Cyprindiol should be stopped immediately and doctor should be contacted if there is a problem with any kind of liver functioning.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8, liver function disturbances are the adverse events reported with use of Co-Cyprindiol.</td>
<td>None</td>
</tr>
<tr>
<td>Use in pregnancy and lactation</td>
<td>The risks of use in pregnancy and lactation are considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in women with known or suspected pregnancy and in breast-feeding women.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Sections 4.4 and 4.6, if pregnancy occurs during treatment with Co-Cyprindiol, further intake must be stopped and mothers who are breast-feeding should be advised not to take Co-Cyprindiol until the nursing mother has weaned her child off breast milk.</td>
<td>None</td>
</tr>
<tr>
<td>Drug interactions leading to breakthrough bleeding or drug failure</td>
<td>The risk of drug interactions leading to breakthrough bleeding or drug failure are considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.5 and PIL Section 2, women on short term treatment or long-term treatment with drugs like antibiotics (e.g. rifampicin, penicillin), anticonvulsants (e.g. barbiturates), should temporarily use a barrier method of contraception</td>
<td>None</td>
</tr>
<tr>
<td>Important potential risks</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Cervical and breast cancer</td>
<td>The risk of cervical and breast cancer are considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.3, ‘and PIL Section 2, Co-Cyprindiol tablets should not be used in patients with presence or history of breast cancer.</td>
<td>None</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Liver tumour</td>
<td>The risk of liver tumour is considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with presence or history of liver tumours (benign or malignant).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Listed in SPC Section 4.8. ‘Undesirable effects’, liver tumours (benign or malignant), are the SAEs reported with Co-Cyprindiol.</td>
<td></td>
</tr>
<tr>
<td>Feminisation of male foetuses</td>
<td>The risk of feminisation of male foetuses is considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.6 and PIL Section 2, pregnancy is an absolute contraindication for treatment with Co-Cyprindiol and must be excluded before such treatment is begun.</td>
<td></td>
</tr>
<tr>
<td>Use in patients with various diseased states</td>
<td>The risk of use in patients with various diseased states (depression, obesity, porphyria, chloasma, cardiovascular diseases, hypertension, migraine, hyperlipidaemia and other conditions/diseases that increase the risk of developing a blood clot) are considered to be adequately addressed in the currently proposed SPC and PIL.</td>
<td>None</td>
</tr>
<tr>
<td>(depression, obesity, porphyria, chloasma, cardiovascular diseases, hypertension, migraine, hyperlipidaemia and other conditions/diseases that increase the risk of developing a blood clot)</td>
<td>• As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with severe or uncontrolled hypertension or hypertension associated with vascular disease.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with severe and/or multiple risk factor(s) for arterial or venous thrombosis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• As per the SPC Section 4.3 and PIL Section 2, Co-Cyprindiol should not be used in patients with severe and/or multiple risk factor(s) for arterial or venous thrombosis.</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
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</tbody>
</table>
| Disturbances of the vaginal bleeding pattern                                 | The risk of disturbances of the vaginal bleeding pattern is considered to be adequately addressed in the currently proposed SPC and PIL.  
  - As per the SPC Section 4.4 and PIL Section 2 and Section 3, if bleeding irregularities persist or occur after previously regular cycles, then adequate diagnostic measures are indicated to exclude malignancy or pregnancy.  
  - As per the SPC Section 4.8 and PIL Section 4, Co-Cyprindiol side-effects related to vaginal bleeding are reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post pill amenorrhoea. | None                                                                                |
| Use in patients with lactose/galactose intolerance                           | The risk of use in patients with lactose/galactose intolerance is considered to be adequately addressed in the currently proposed SPC and PIL.  
  - As per the SPC Section 4.4 and PIL Section 2, the patient with lactose/galactose tolerance should not take this medicine.                                        | None                                                                                |
| Interference with laboratory tests                                           | The risk of interference with results of laboratory tests is considered to be adequately addressed in the currently proposed SPC and PIL.  
  - As per the SPC Section 4.5 and PIL Section 2, as use of Co-Cyprindiol may affect the results of certain laboratory tests, the laboratory staff or the doctor should always be informed if the patient is taking Co-Cyprindiol. | None                                                                                |
IV.7  Discussion on the clinical aspects
With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Cyproterone acetate 2.0 mg and Ethinylestradiol 0.035 mg tablets and the reference product DIANE® 35 microgram tablets (Bayer Schering Pharma), under fasting conditions.

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 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 product is acceptable, and no new non-clinical or clinical concerns have been identified. Bioequivalence has been demonstrated between the applicant’s product and the reference product. Extensive clinical experience with ciproterone acetate and ethinylestradiol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk 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 (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Teragezza 2000/35 microgram Film-coated Tablets is presented below:
Each film-coated tablet contains 2 mg Cyproterone acetate and 35 micrograms Ethinylestradiol.

Contains Lactose. Read the package leaflet for further information.

For oral use.

Read the package leaflet before use.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Store in the original package in order to protect from light.

M4 Health: Morningside HealthCare Ltd
115 Narborough Road, Leicester
LE3 0PA, UK
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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