CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Ethinylestradiol 0.035 mg /Cyproteronacetaat 2 mg, coated tablets Stragen Nordic A/S, Denmark

# ethinylestradiol / cyproteroneacetate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/0623/001/MR**
**Registration number in the Netherlands: RVG 29728**

**Date of first publication: 26 August 2008**
**Last revision: 16 August 2010**

| | |
|---|---|
| Pharmacotherapeutic group: | Antiandrogens and estrogens |
| ATC code: | G03HB01 |
| Route of administration: | oral |
| Therapeutic indication: | treatment of severe acne, with or without seborrhoea; refractory to prolonged oral antibiotic therapy; treatment of mild hirsutism |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 20 December 2004 |
| Concerned Member States: | Mutual recognition procedure with CZ, DE, DK, FI, HU, NO, PL and SK. |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(1) |

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Ethinylestradiol 0.035 mg/Cyproteronacetaat 2 mg, coated tablets, from Stragen Nordic A/S. The date of authorisation was on 20 December 2004 in the Netherlands. The product is indicated for use in women for treatment of severe acne, with or without seborrhoea, refractory to prolonged oral antibiotic therapy, and for mild hirsutism. Although this medicinal product also acts as an oral contraceptive, it should only be used in patients requiring hormone treatment for the above conditions. This medicinal product is not recommended to be used for contraception only.

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

Cyproteroneacetate blocks androgen-receptors and thereby reduces the influence of androgens on androgen-dependent organs. Apart from this anti-androgen effect cyproteroneacetate also shows a strong progestagenic and antigonadotropic effect. Using cyproteroneacetate enables to decrease or eliminate the signs of virilisation in women, whether the origin is an increased antrogen level or an increased peripheral sensitivity for androgens.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Diane-35, coated tablets (NL License RVG 11903), containing 0.035 ethinylestradiol and 2 mg cyproteroneacetate, which has been registered in the Netherlands by Bayer B.V. since 1987. In addition, reference is made to Diane-35 authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Diana-35, registered in France. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

**Active substance and excipients**
The active substances are ethinylestradiol and cyproteroneacetate, established active substances described in the European Pharmacopoeia (Ph.Eur.*). The drug substance cyproteroneacetate is a white or almost white crystalline powder, practically insoluble in water, very soluble in methylene chloride and freely soluble in acetone. The drug substance ethinylestradiol is a white or slightly yellowish-white crystalline powder, practically insoluble in water. The active substance specifications for ethinylestradiol and cyproteroneacetate are considered adequate to control the quality and both meet the requirements of their respective monograph in the Ph.Eur. Furthermore, for cyproteroneacetate additional specifications for related substances and residual solvents are set.
Batch analytical data demonstrating compliance with the specifications have been provided for 3 production scaled batches for cyproteroneacetate and for 3 production scaled batches for ethinylestradiol.

The Active Substance Master File (ASMF) procedure is used for the active substance cyproteroneacetate. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the active substance ethinylestradiol. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur. After authorisation an additional supplier for ethinylestradiol was added (see also 'Steps taken after the finalisation of the initial procedure' on page 10).

Stability data on the active substance cyproteroneacetate have been provided for 3 full-scale batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. Based on the data submitted, 12 months extrapolation is acceptable and a retest period was granted of 3 years when stored in double LD-PE bags inside fibre board drums without further storage conditions.
The active substance ethinylestradiol is stable for 3 years without further storage conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The used excipients are commonly used in sugar coated, immediate release tablets. The excipients are safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs, except for montan glycol wax for which reference is made to the German Pharmacopoeia (DAB).

**Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

**Medicinal Product**

Composition

Ethinylestradiol 0.035 mg/ Cyproteronacetaat 2 mg, coated tablets contain as active substances 0.035 mg ethinylestradiol and 2 mg of cyproteroneacetate, and are white, round, biconvex coated tablets.

The tablets are packed in blister memo packs, made of PVC /aluminium foil.

The excipients are:
*Tablet core* - lactose monohydrate, maize starch, povidone K25 (E1201), magnesium stearate (E 470B), talc (E553B),
*Coating* - sucrose, calcium carbonate (E 170), macrogol 6,000, talc (E553B), titanium dioxide (E 171), povidone K90 ((E1201), glycerol 85% (E422), montan glycol wax (E912).

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Diane-35, coated tablets.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 full-scale production batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, diameter, height, average weight, mass uniformity, disintegration time, loss on drying, uniformity of content, dissolution rate and microbiological purity. For identification, assay, related substances of both active substances an in-house HPLC-method is used. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the product have been provided for 3 full-scale production batches in accordance with applicable European guidelines demonstrating the stability of the product over 36 months. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions need to be included in the SPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

## II.2 Non-clinical aspects

This product is a generic formulation of Diane-35, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ethinylestradiol and cyproteroneacetate

released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Ethinylestradiol and cyproteroneacetate are well-known active substances with an established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Diane-35 marketed by Bayer B.V., except for some additional advice in section 4.2 of the SPC, which was decided during the MRP. This additional information concerned the lengths of treatment and advice on stopping treatment because of insufficient clinical effect:

- It is recommended that treatment be withdrawn 3 to 4 cycles after the indicated condition(s) has/have completely resolved and that Ethinylestradiol 0.035 mg/ Cyproteronacetaat 2 mg is not continued solely to provide oral contraception.
- Therapy should be reconsidered if therapy is inadequate or fails in the following cases:
    - severe acne or seborrhoea after at least six months of therapy
    - hirsutism after at least 12 months of therapy

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Ethinylestradiol/cyproteroneacetate 0.035/2 mg tablet is compared with the pharmacokinetic profile of the French reference product Diana-35 tablet.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 35 post-menopausal female volunteers, aged 47-63 years. Each subject received two tablets of one of the 2 ethinylestradiol/cyproteroneacetate formulations. The tablets were orally administered with 240 ml water after an overnight fast. For each subject there were 2 dosing periods, separated by a washout period of 28 days. Two subjects were withdrawn from the study. One subject was withdrawn due to adverse events and one subject was withdrawn due to a personal reason. The bioavailability of the test Ethinylestradiol/cyproteroneacetate 0.035/2 mg tablet was compared to the French reference product Diana-35 tablet (Bayer, France). Blood samples for the determination of cyproteroneacetate were taken pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 12, 24, 48, 72, 96, 120, 144, 168 and 192 h after administration. Blood samples for the determination of ethinylestradiol were taken pre-dose and at 0.5. 1, 1.5, 2, 2.5, 3, 3.5, 4, 12, 24, 48, and 72 hours after administration. Statistical and pharmacokinetic analysis was performed on 30 subjects.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of cyproteroneacetate under fasted conditions.

| **Treatment N=30** | **$AUC_{0-t}$** pg.h/ml | **$AUC_{0-\infty}$** pg.h/ml | **$C_{max}$** pg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 318206 ± 78627 | 403150 ± 116224 | 27436 ± 5873 | 2.00 ± 0.00 | 103.55 ± 24.84 |
| **Reference** | 327887 ± 85063 | 428493 ± 132888 | 2994 ± 7268 | 1.50 ± 0.50 | 116.80 ± 38.68 |
| ***Ratio(90% CI)** | 0.97 (0.94-1.00) | 0.95 (0.91-0.98) | 0.92 (0.92-1.09) | -- | -- |
| **CV (%)** | 7.3 | 9.2 | 14.5 | -- | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of ethinylestradiol under fasted conditions.

| **Treatment N=30** | **$AUC_{0-t}$** pg.h/ml | **$AUC_{0-\infty}$** pg.h/ml | **$C_{max}$** pg/ml | **$t_{max}$** h | **$t_{1/2}$** h |
|---|---|---|---|---|---|
| **Test** | 2044 ± 761 | 2275 ± 849 | 169 ± 52 | 2.00 ± 0.75 | 16.07 ± 4.76 |
| **Reference** | 2027 ± 613 | 2229 ± 683 | 177 ± 59 | 2.00 ± 0.50 | 16.81 ± 5.39 |
| ***Ratio(90% CI)** | 0.99 (0.92-1.05) | 1.00 (0.94-1.07) | 0.96 (0.92-1.00) | -- | -- |
| **CV (%)** | 14.9 | 15.2 | 9.8 | -- | -- |

| | |
|---|---|
| **$AUC_{0-\infty}$** | area under the plasma concentration-time curve from time zero to infinity |
| **$AUC_{0-t}$** | area under the plasma concentration-time curve from time zero to t hours |
| **$C_{max}$** | maximum plasma concentration |
| **$t_{max}$** | time for maximum concentration |
| **$t_{1/2}$** | half-life |

**ln-transformed values*

The combination of ethinylestradiol and cyproteronacetate should be taken once daily without reference to food intake. From the literature it is known that food does not interact with the absorption of ethinylestradiol and cyproteroneacetate. Therefore, a food interaction study is not deemed necessary.

The 90% confidence intervals calculated for $AUC_{0-inf}$, $AUC_{0-t}$, and $C_{max}$ of ethinylestradiol acetate and the $AUC_{0-t}$, and $C_{max}$ of cyproterone acetate are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of ethinylestradiol and cyproteroneacetate under fasted conditions, it can be concluded that Ethinylestradiol/cyproteronacetaat 0.035/2 mg tablet and the French reference product Diana-35 tablet are bioequivalent with respect to the extent and rate of absorption. And fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Due to its relatively long terminal half-life the extrapolation of the $AUC_{0-inf}$ of cyproteroneacetate was more than 20% in most cases. This is considered of no importance because sampling was performed over 192 hours and absorption is supposed to be completed over this time range.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Readability test

At the time of first registration a readability test was not required; therefore the absence of a readability test is accepted.

Risk Management Plan

Ethinylestradiol and cyproteronacetate were first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profiles of ethinylestradiol and cyproteronacetate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ethinylestradiol 0.035 mg /Cyproteronacetaat 2 mg, coated tablets, has a proven chemical-pharmaceutical quality and is a generic form of Diane-35. Diane-35 is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH. Additional advice on the duration of treatment was added to the SPC during the MRP.

The Board followed the advice of the assessors. Ethinylestradiol 0.035 mg /Cyproteronacetaat 2 ml is authorised in the Netherlands on 20 December 2004.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Ethinylestradiol 0.035 mg/Cyproteronacetaat 2 mg with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 8 December 2005.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from 8 December 2005 until 8 December 2008.

The date for the first renewal will be: 8 December 2010.

There were no post-approval commitments made during the procedure.

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of procedure | Approval/non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Submission of an additional supplier of the active substance. | NL/H/0623/001/II/001 | II | 16-2-2006 | 2-6-2006 | Approval | N |
| Change in the name of the medicinal product. | NL/H/0623/001/IB/002 | IB | 21-9-2006 | 23-10-2006 | Approval | N |
| Change in the name and/or address of the MAH. | NL/H/0623/001/IA/003 | IA | 15-9-2006 | 21-9-2006 | Approval | N |
| Change in the name of the medicinal product. | NL/H/0623/001/IB/004 | IB | 21-12-2006 | 20-1-2007 | Approval | N |
| Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved. | NL/H/0623/001/IA/005 | IA | 9-8-2007 | 23-8-2007 | Approval | N |
| Addition of a manufacturer responsible for batch release; not including batch control/testing. | NL/H/0623/001/IA/006 | IA | 20-5-2009 | 3-6-2009 | Approval | N |
| Deletion of any manufacturing site. | NL/H/0623/001/IA/007 | IA | 20-5-2009 | 3-6-2009 | Approval | N |
| Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved. | NL/H/0623/001/IA/008 | IA | 20-5-2009 | 3-6-2009 | Approval | N |
| Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier. | NL/H/0623/001/IA/012 | IA | 9-7-2010 | 8-8-2010 | Approval | N |