Safeguarding public health

MHRA

Public Assessment Report

Clairette 2000/35 Tablets

(cyproterone acetate / ethinylestradiol)

PL 14838/0004

Medicines and Healthcare products Regulatory Agency

CLAIRETTE 2000/35 TABLETS

(CYPROTERONE ACETATE / ETHINYLESTRADIOL) PL 14838/0004

UKPAR

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CLAIRETTE 2000/35 TABLETS

(CYPROTERONE ACETATE / ETHINYLESTRADIOL) PL 14838/0004

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Harefield Pharma Associates Limited a Marketing Authorisation (licence) for the medicinal product Clairette 2000/35 Tablets (PL 14838/0004). This is a prescription only medicine [POM] used, in women only, to treat severe acne that has not improved after long term treatment with oral antibiotics, or to treat excessive hair on the face or body.

Although Clairette 2000/35 Tablets can act as an oral contraceptive, it is not to be used in women solely for this purpose. Rather, it should only be used for contraception in women who require treatment for the skin conditions described above.

In women, the ovaries have to make male sex hormones (androgens) which are then changed into female sex hormones (oestrogens). Androgens help the skin to grow but can also cause very greasy skin, leading to blockage of the grease glands which may then become infected and inflamed, resulting in acne spots. Androgens may also cause more growth of hair on the face and body.

Clairette 2000/35 Tablets contain the active ingredients cyproterone acetate and ethinylestradiol. These ingredients block the receptors by means of which androgens act and also reduce the amount of androgens available by cutting down its production.

The clinical data presented to the MHRA, before licensing, demonstrated that Clairette 2000/35 Tablets is essentially similar or equivalent to the approved product, Dianette Tablets, and as such can be used interchangeably.

No new or unexpected safety concerns arose from this application and it was decided that the benefits of using Clairette 2000/35 Tablets outweigh the risks, hence a Marketing Authorisation has been granted.

CLAIRETTE 2000/35 TABLETS

(CYPROTERONE ACETATE / ETHINYLESTRADIOL) PL 14838/0004

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Clairette 2000/35 Tablets (PL 14838/0004) to Harefield Pharma Associates Limited on 8 February 2006. The product is a prescription only medicine.

The application was submitted as an abridged application according to Article 10.1(a)(iii) of Directive 2001/83/EC as amended, claiming essential similarity to Dianette Tablets (PL 00053/0190), granted 11 June 1987.

The product contains the active ingredients cyproterone acetate and ethinylestradiol in a combination also known as Co-cyprindiol Tablets.

Clairette 2000/35 Tablets is indicated for use, in women only, to treat (a) severe acne, refractory to prolonged oral antibiotic therapy; (b) moderately severe hirsutism. Although Clairette 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.

Clairette 2000/35 blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitiary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

PHARMACEUTICAL ASSESSMENT

PL Number:	**PL 14838/0004**
Name of Product:	**Clairette 2000/35 Tablets**
Actives:	**Cyproterone Acetate (CPA) and Ethinylestradiol (EE)**
Company Name:	**Harefield Pharma Associates Ltd**
E.C. Directive:	**2001/83/EC Article 10.1(a)(iii)**
Legal Status:	**POM**

INTRODUCTION

Legal Basis

This is a national complex abridged application for Clairette 2000/35 Tablets, submitted under Article 10.1(a)(iii) of Directive 2001/83/EC as amended, claiming essential similarity to Dianette coated tablets (PL 00053/0190, granted 11 June 1987), marketed by Schering Healthcare Ltd., UK. The original product Diane 35 was authorised in France in 1987, and is also used in the bioequivalence study.

The fee category is complex abridged, this is accepted as the active substance cyproterone acetate is from a new source not previously approved in the UK licensed product.

Use

The tablets are indicated for use in women only for the treatment of (a) severe acne, refractory to prolonged oral antibiotic; (b) moderately severe hirsutism.

Clairette 2000/35 Tablets should not be used in women solely as oral contraceptive.

TSE

Section 2.6.2 of the marketing authorisation application (MAA) form states that lactose monohydrate is the only ingredient of animal origin and satisfactory TSE statements are provided for lactose monohydrate, magnesium stearate, Glycerol 85%, and Montan glycol wax. The latter three are confirmed as being derived from plant sources.

The product is therefore Annex II according to MCA letter dated 7 July 2000.

Background

Other generic licences approved for Co-cyprindiol tablets are from Sandoz (PL 04416/0465), Stiefel Laboratories, as Acnediol, (PL 00174/0221), Neolab (PL 08137/0081) and Generics (UK) (PL 04569/0486).

This application is presented in the CTD format.

DRUG SUBSTANCE

Cyproterone acetate

A source of active substance is proposed. The active from this source is the subject of a drug master file (DMF). Full assessment of the DMF was carried out during the review of a previously granted UK licence.

A copy of the current DMF edition of the applicant's part has been provided in the CTD format. A letter of access is provided**.**

A satisfactory drug substance specification is included in the DMF.

The finished product manufacturer has also provided a drug substance specification. Certificates of Analysis (CoAs) for batches of the drug substance tested on receipt have been provided.

Stability
This is satisfactorily addressed in the DMFs.

Ethinylestradiol

A source of active substance is proposed. The active from this source is the subject of a DMF in CTD format. Full assessment of the DMF was carried out.

A copy of the current DMF edition of the applicant's part has been provided in the CTD format. A letter of access is provided**.**

A satisfactory drug substance specification is included in the DMF.

The finished product manufacturer has also provided a drug substance specification.

Analytical Procedures
Analytical procedures are described.

Validation of Analytical Procedures
Satisfactory validation data are provided for the analytical procedures.

Batch Analysis
Results of industrial scale batches of ethinylestradiol are within specification.

Reference standards
Satisfactory primary and working reference standards are identified.

Stability
Batches stored at real time and accelerated conditions showed no degradation.

DRUG PRODUCT

Composition of the medicinal product

The composition is satisfactorily summarised in the Quality Overall Summary. The active ingredients are Cyproterone Acetate Ph.Eur. 2.00mg and Ethinylestradiol Ph.Eur. 0.035mg. The product also contains the following excipients: Lactose Monohydrate Ph.Eur., Maize Starch Ph.Eur., Povidone K25 Ph.Eur., Magnesium Stearate* Ph.Eur., Talc Ph.Eur., Sucrose Ph.Eur., Calcium Carbonate Ph.Eur., Polyethylene Glycol 6000 Ph.Eur., Titanium dioxide Ph.Eur., Povidone K90 Ph.Eur., Glycerin 85%* Ph.Eur., Wax, Montan Glycol* DAB, and Purified Water Ph.Eur. (not present in final product).

*Derived from plant sources.

Development Pharmaceutics

Drug substances
Cyproterone acetate is practically insoluble in water and does not show polymorphism. Ethinylestradiol is also practically insoluble in water and shows no polymorphism.

Excipients
The excipients chosen for the Co-cyprindiol tablets are the same as in the commercially available Diane 35 tablets (Schering). The formulation is sugar-coated tablets, comprising of excipients that comply with Ph.Eur., except the Montan glycol that complies with the German Pharmacopoeia (DAB). The function and concentration of the excipients used is standard and accepted.

Pharmacokinetic studies
The objective of the study was to compare the rate and extent of absorption of Co-cyprindiol tablets (test) versus Diane 35 tablets from Schering (reference), administered under fasting conditions. The French Diane 35 tablets are qualitatively and quantitatively similar to the UK licensed Dianette tablets (PL 00053/0190).

Satisfactory CoAs are provided for the biobatches.

Thirty five (35) healthy volunteers were included in a two-way cross randomised crossover bioequivalence study and the first 30 subjects were analysed as per protocol. The two treatment periods were separated by an acceptable wash-out period.

The sampling period is considered suitable. The ratio of $AUC_{0-t}/AUC_{0-\infty}$ for the test and reference is around >0.80 for EE and >0.75 for CPA (30 subjects), but >0.80 for CPA (12 subjects).

Plasma concentrations of CPA were determined using validated methods. Limits of detection and quantitation are given.

The pharmacokinetic parameters (t_{max}, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) were determined for the test and reference products. The two formulations were compared by ANOVA applied to log transformed data. Bioequivalence was demonstrated for the C_{max} and AUCs using 90% CI

around test/reference ratios. For the t_{max}, a non-parametric method was used. The data are given below:

Pharmacokinetics parameters of ethinylestradiol (n=30)			
Parameters	Test product	Diane 35®	90% CI*
AUC_{0-t} (pg.h/ml)	2044.33 ± 761.49	2026.55 ± 612.80	92.21 – 104.66
$AUC_{0-\infty}$(pg.h/ml)	2274.66 ± 849.00	2229.14 ± 682.69	93.40 – 106.27
C_{max} (pg/ml)	169.22 ± 52.09	177.48 ± 58.72	91.94 – 100.29
$t_{½}$ (h)	16.07 ± 4.76	16.81 ± 5.39	
t_{max} (h)	2.0 ± 0.75	2.00 ± 0.50	

Pharmacokinetics parameters of cyproterone acetate (n=30)			
Parameters	Test product	Diane 35®	90% CI*
AUC_{0-t} (pg.h/ml)	318206.1 ± 78626.9	327887.3 ± 85063.0	94.08 – 100.15
$AUC_{0-\infty}$ (pg.h/ml)	403149.9 ± 116224.5	428492.9 ± 132888.0	90.70 – 97.75
C_{max} (pg/ml)	27436.24 ± 5872.79	29942.10 ± 7268.07	86.23 – 97.63
$t_{½}$ (h)	103.55 ± 24.84	116.80 ± 38.68	
t_{max} (h)	2.00 ± 0.00	1.50 ± 0.50	

*90% geometric Confidence Interval using ln-transformed data.

The bioavailability parameters ($AUC_{0-\infty}$, AUC_{0-t} and C_{max}) were within the 90% CI limit of 0.80-1.25. Therefore, the two products are considered bioequivalent, in line with Notes for Guidance (NfG) CPMP/EWP/QWP/1401/98 "The Investigation of Bioavailability and Bioequivalence".

Container closure system
The container is the blister pack, PVC 250µm/Aluminium 20µm foil with heat seal lacquer, with 1 or 3 strips of 21 tablets in a carton (21 or 63 tablets).

Data are provided for the primary packaging to show compliance with Directive 90/128/EEC.

Microbiological attributes
Stated 'not relevant'. The microbiological attributes are controlled in the finished product specification to Ph.Eur. 5.1.4 category 3A and accepted.

Compatibility
Stated 'not relevant' but can be inferred from the product stability data, and accepted.

Manufacture

GMP Statement and Manufacturing Chain
The site of batch release is Haupt Pharma, Schleebruggenkamp 15, 48159 Munster, Germany. The sites of manufacture and assembly are also stated. A satisfactory copy of manufacturing licence, Nr.59/24.2.41.1-52/23.11.0102.5, issued on 17 December 1999 by The Regional Government of Munster is provided.

This site has been approved for the manufacture of other UK licensed products.

Description of the Manufacturing Process
A satisfactory formula, flow diagram and description of manufacture are provided. There are no re-processing data provided.

Critical phases of the manufacturing process have been satisfactorily identified and appropriate in-process controls are in place.

The analytical methods and limits are the same as those used in finished product testing and comply with current guidelines and accepted. The tablets are blister packed with satisfactory in-process controls.

In-process batch data for validation batches are satisfactory. The validation results demonstrate homogeneity of blends and consistent manufacture.

The validation protocol provided is considered adequate for their purpose.

Control of Excipients

Excipients included in a Pharmacopoeia
The list of excipients, complying with Ph.Eur. requirements, is given under "Composition of the medicinal product" above. Montan glycol complies with the German Pharmacopoeia (DAB).

None of the excipients are TSE risk materials. Magnesium stearate, glycerol and montan glycol wax are derived from plant sources.

Satisfactory Certificates of Analysis have been provided for each excipient and are accepted. The compendial methodology is used in testing.

Control of Drug Product

Specifications
A satisfactory finished product specification is provided.

Analytical procedures
Satisfactory methodology validation data are provided.

Batch data
Satisfactory data are provided for batches manufactured at the proposed site and are considered representative of the product to be marketed. Dissolution data including standard deviations and profiles are reported.

Characterisation of impurities
This is satisfactory. The drug substances are known to be stable and are confirmed by the stress studies.

Reference Samples
Reference samples are identified.

Container/closure system

Satisfactory details of supplier specification, product construction, standards and compliance statements (90/128/EEC, as amended) as well as IR spectrum of polymer film and DIN safety data are provided. In-house specification giving details of tests performed on receipt are provided.

Stability of Drug Product

Standard storage conditions
Based on stability data at normal and accelerated conditions, a shelf life of 36 months for the tablets packed in Al/PVC blisters with no special storage conditions, is proposed and accepted.

The stability programme complies with current ICH guidelines, NfG CPMP/QWP/556/96 "Stability Testing on Active Substances and Finished Products".

The samples provided for stability studies are representative of the product to be marketed in the proposed pack.

The programme is to last for 60 months. The stability programme is satisfactory.

The results of the stability studies support the proposed shelf life.

Bioanalytical methods and validation

Satisfactory methodology and validation data are provided.

Quality overall summary

This is satisfactory.

Essential similarity

The following data support essential similarity:

a) Acceptable bioequivalence between test and reference product.
b) Comparative dissolution profiles are provided for test and reference product.
c) The impurity profile of the test product is comparable with that of the reference product and considered satisfactory. The impurities comply with the ICH guidelines.
d) The active substances conform to Ph.Eur. requirements and complies with the ICH guidelines.

PRODUCT PARTICULARS

Product brand name

This is considered satisfactory.

Summary of Product Characteristics

Satisfactory SPC provided.

Patient information leaflet

Satisfactory coloured mock-up is provided**.** The applicant has until 1 July 2008 to amend the order in which the information appears in the leaflet and provide user testing data (both parts of Article 59, Directive 2004/27/EC must be complied with at the same time).

Labelling

Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) form

This is satisfactory.

ADDITIONAL DATA REQUIREMENTS

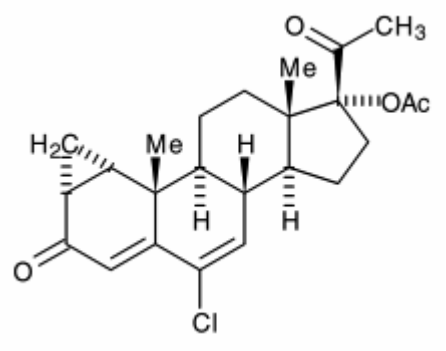
Satisfactory.

CONCLUSION

A product licence may be granted for this product.

APPENDIX A

Cyproterone acetate Ph Eur Monograph



$C_{24}H_{29}ClO_4$ 416.9 *427-51-0*

Cyproterone Acetate complies with the requirements of the 3rd edition of the European Pharmacopoeia [1094]. These requirements are reproduced after the heading 'Definition' below.

Action and use Antiandrogen.

Ph Eur

DEFINITION

Cyproterone acetate contains not less than 97.0 per cent and not more than the equivalent of 103.0 per cent of 6-chloro-17-hydroxy- 1a, 2a-methylenepregna-4, 6-diene-3, 20-dione 17-acetate, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, very soluble in methylene chloride, freely soluble in acetone, soluble in methanol, sparingly soluble in ethanol.

It melts at about 210°C.

IDENTIFICATION

First identification: A.

Second identification: B, C, D, and E.

A. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *Cyproterone acetate CRS*.

B. Examine by thin-layer chromatography (*2.2.27*), using a *TLC silica gel F_{254} plate R*.

Test solution. Dissolve 20 mg of the substance to be examined in *methylene chloride R* and dilute to 10 ml with the same solvent.

Reference solution. Dissolve 10 mg of *Cyproterone acetate CRS* in *methylene chloride R* and dilute to 5 ml with the same solvent.

Apply to the plate 5 µl of each solution. Develop over a path of 15 cm using a mixture of equal volumes of *cyclohexane R* and *ethyl acetate R.* Allow the plate to dry in air. Repeat the development. Allow the plate to dry in air. Examine in ultraviolet light at 254 nm. The principal spot in the chromatogram obtained with the test solution is similar in position and size to the principal spot in the chromatogram obtained with the reference solution.

C. To about 1 mg add 2 ml of *sulphuric acid R* and heat on a water-bath for 2 min. A red colour develops. Cool. Add the solution cautiously to 4 ml of *water R* and shake. The solution becomes violet.

D. Incinerate about 30 mg with 0.3 g of *anhydrous sodium carbonate R* over a naked flame for about 10 min. Cool and dissolve the residue in 5 ml of *dilute nitric acid R*. Filter. To 1 ml of the filtrate add 1 ml of *water R*. The solution gives reaction (a) of chlorides (*2.3.1*).

E. It gives the reaction of acetyl (*2.3.1*).

TESTS

Specific optical rotation (*2.2.7*). Dissolve 0.25 g in *acetone R* and dilute to 25.0 ml with the same solvent. The specific optical rotation is +152° to +157°, calculated with reference to the dried substance.

Related substances Examine by liquid chromatography (*2.2.29*).

Test solution. Dissolve 10.0 mg of the substance to be examined in *acetonitrile R* and dilute to 10.0 ml with the same solvent.

Reference solution (a). Dilute 1.0 ml of the test solution to 100.0 ml with *acetonitrile R*.

Reference solution (b). Dissolve 5 mg of *medroxyprogesterone acetate CRS* in *acetonitrile R* and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of the solution to 10.0 ml with reference solution (a).

The chromatographic procedure may be carried out using:

A stainless steel column 0.125 m long and 4.6 mm in internal diameter packed with *octadecylsilyl silica gel for chromatography R* (3 µm),

As mobile phase at a flow rate of 1.5 ml/min a mixture of 40 volumes of *acetonitrile R* and 60 volumes of *water R*,

As detector a spectrophotometer set at 254 nm.

Inject 20 µl of reference solution (a) and 20 µl of reference solution (b). Adjust the sensitivity of the system so that the height of the principal peak in the chromatogram obtained with reference solution (a) is at least 50 per cent of the full scale of the recorder. The test is not valid unless, in the chromatogram obtained with reference solution (b), the resolution between the peak corresponding to Cyproterone acetate and the peak corresponding to medroxyprogesterone acetate is at least 3.0.

Inject 20 µl of the test solution. Continue the chromatography for twice the retention time of Cyproterone acetate. In the chromatogram obtained with the test solution, the sum of the areas of all the peaks, apart from the principal peak, is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent). Disregard any peak with an area less than 0.05 times that of the principal peak in the chromatogram obtained with reference solution (a).

Loss on drying (*2.2.32*). Not more than 0.5 per cent, determined on 1.000 g by drying at 80°C at a pressure not exceeding 0.7 kPa.

Sulphated ash (*2.4.14*). Not more than 0.1 per cent, determined on 1.0 g.

ASSAY

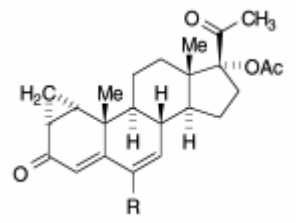
Dissolve 50.0 mg in *methanol R* and dilute to 50.0 ml with the same solvent. Dilute 1.0 ml of the solution to 100.0 ml with *methanol R*. Measure the absorbance (*2.2.25*) at the maximum at 282 nm.

Calculate the content of $C_{24}H_{29}ClO_4$ taking the specific absorbance to be 414.

STORAGE

Store protected from light.

IMPURITIES

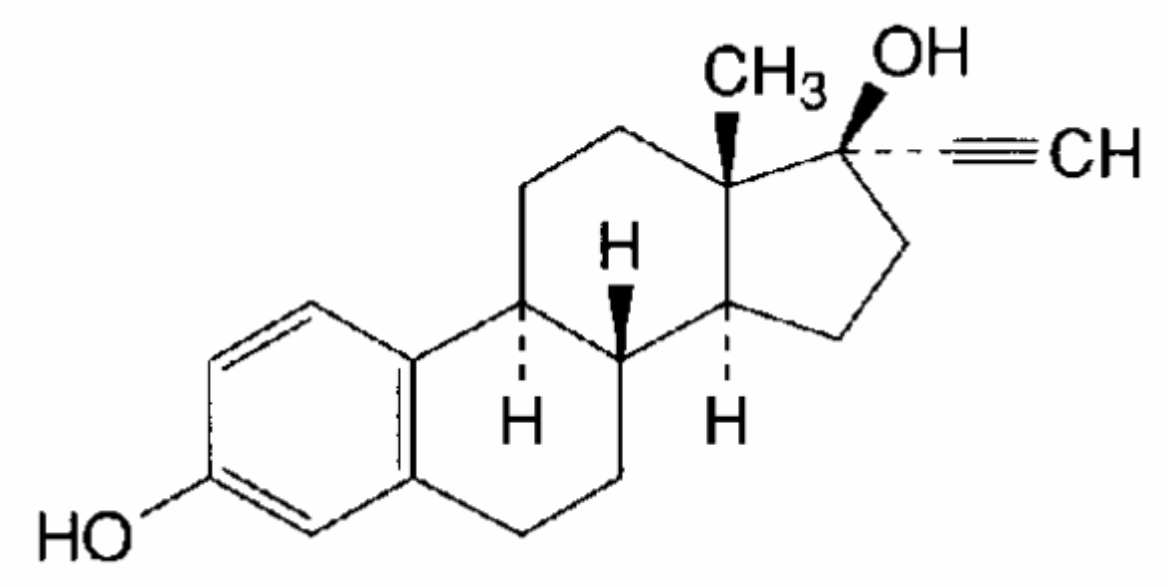


A. R = H: 17-hydroxy-1a, 2a-methylenepregna-4, 6-diene-3, 20-dione-17-acetate,

B. R = OCH_3: 17-hydroxy-6-methoxy-1a, 2a-methylenepregna-4, 6-diene-3, 20-dione-17 -acetate.

APPENDIX A

Ethinylestradiol Ph Eur Monograph 0140



$C_{20}H_{24}O_2$ 296.4 57-63-6

Ph Eur

DEFINITION
19-Nor-17a-pregna-1,3,5(10)-trien-20-yne-3,17-diol.

Content
97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance
White or slightly yellowish-white, crystalline powder.

Solubility
Practically insoluble in water, freely soluble in alcohol. It dissolves in dilute alkaline solutions.

IDENTIFICATION
A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison
Ethinylestradiol CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance in *methanol R*, evaporate to dryness and record new spectra using the residues.

B. Thin-layer chromatography (*2.2.27*).
Test solution

Dissolve 25 mg of the substance to be examined in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 25 ml with the same mixture of solvents.

Reference solution
Dissolve 25 mg of *ethinylestradiol CRS* in a mixture of 1 volume of *methanol R* and 9 volumes of *methylene chloride R* and dilute to 25 ml with the same mixture of solvents.

Plate
TLC silica gel G plate R.

Mobile phase
Alcohol R, *toluene R* (10:90 V/V).

Application
5 µl.

Development
Over a path of 15 cm.

Drying
In air until the solvent has evaporated.

Detection
Heat at 110 °C for 10 min, spray the hot plate with *alcoholic solution of sulphuric acid R* and heat again at 110 °C for 10 min. Examine in daylight and in ultraviolet light at 365 nm.

Results
The principal spot in the chromatogram obtained with the test solution is similar in position, colour, fluorescence and size to the principal spot in the chromatogram obtained with the reference solution.

TESTS
Specific optical rotation (*2.2.7*)
- 27 to - 30 (dried substance).

Dissolve 1.25 g in *pyridine R* and dilute to 25.0 ml with the same solvent.

Related substances
Liquid chromatography (*2.2.29*).

Test solution
Dissolve 0.10 g of the substance to be examined in the mobile phase and dilute to 100.0 ml with the mobile phase.

Reference solution (a)
Dissolve 10 mg of *estradiol R* in the mobile phase, add 10.0 ml of the test solution and dilute to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 10.0 ml with the mobile phase.

Reference solution (b)

Dilute 10.0 ml of the test solution to 50.0 ml with the mobile phase. Dilute 1.0 ml of this solution to 20.0 ml with the mobile phase.

Column:
size: *l* = 0.15 m, Ø = 4.6 mm,
stationary phase: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase
Acetonitrile R, *water R* (45:55 *V/V*).

Flow rate
1 ml/min.

Detection
Spectrophotometer at 280 nm.

Injection
20 µl.

Run time
2.5 times the retention time of ethinylestradiol.

Relative retention
With reference to ethinylestradiol (retention time = about 4.6 min): impurity D = about 0.76, impurity B = about 0.94.

System suitability
Reference solution (a):

resolution: minimum 3.5 between the peaks due to impurity D and ethinylestradiol.
Limits:
impurity B: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent),

any other impurity: not more than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.25 per cent),

total of other impurities: not more than half the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent)

disregard limit: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent)

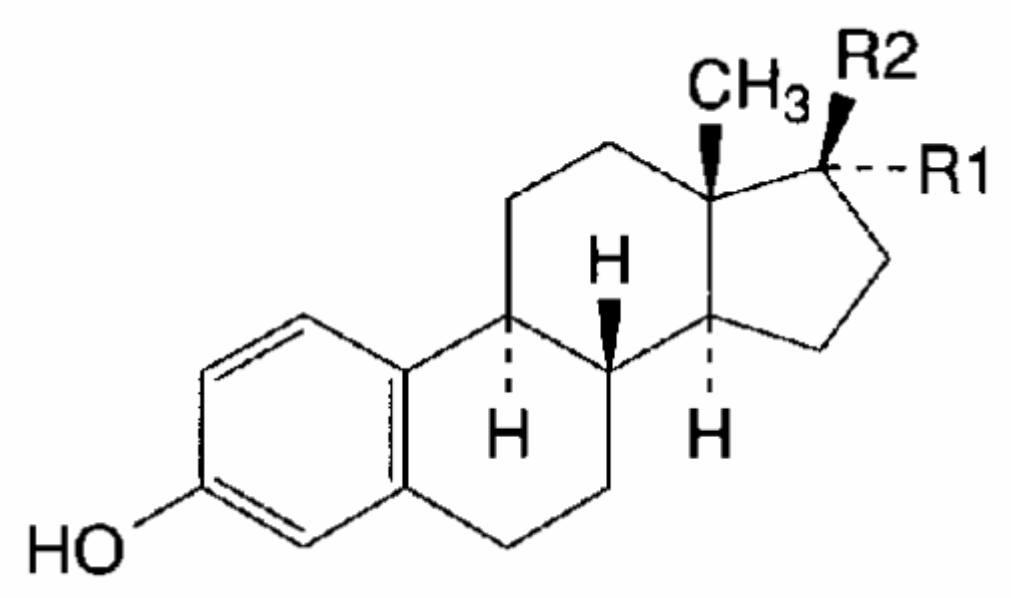
Loss on drying (*2.2.32*)
Maximum 1.0 per cent, determined on 0.500 g by drying in an oven at 100–105 °C for 3 h.

ASSAY
Dissolve 0.200 g in 40 ml of *tetrahydrofuran R* and add 5 ml of a 100 g/l solution of *silver nitrate R*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

1 ml of *0.1 M sodium hydroxide* is equivalent to 29.64 mg of $C_{20}H_{24}O_2$.

STORAGE
Protected from light.

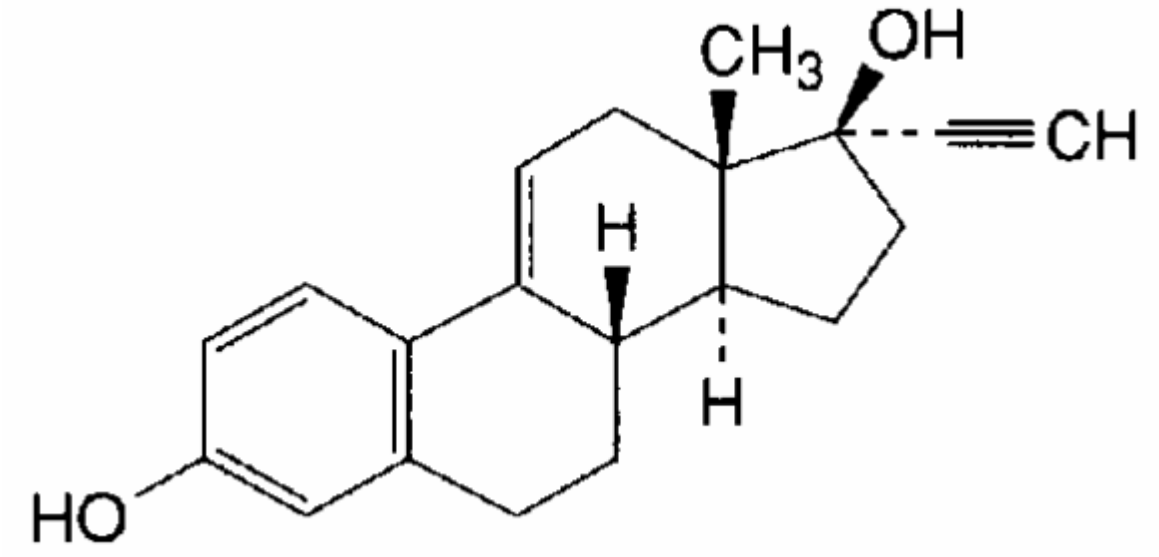
IMPURITIES



A. R1 = OH, R2 = CºCH: 19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol (17b-ethinylestradiol),

C. R1 + R2 = O: 3-hydroxyestra-1,3,5(10)-trien-17-one (estrone),

D. R1 = H, R2 = OH: estradiol,



B. 19-nor-17a-pregna-1,3,5(10),9(11)-tetraen-20-yne-3,17-diol.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

LICENCE NO:	**PL 14838/0004**
PROPRIETARY NAME:	**Clairette 2000/35 Tablets**
ACTIVE(S):	**Cyproterone acetate and ethinylestradiol**
COMPANY NAME:	**Harefield Pharma Associates Limited**
E.C. ARTICLE:	**10.1(a)(iii)**
LEGAL STATUS:	**POM**

INTRODUCTION

This is a national abridged complex application requesting a marketing authorisation for Clairette 2000/35 Tablets, PL 14838/0004. The applicant claims essential similarity to the UK brand leader, Dianette tablets (PL 00053/0190), licensed to Schering Health Care Ltd and first granted in June 1987. The application was made under article 10.1(a)(iii) of EC Directive 2001/83.

BACKGROUND

Clairette 2000/35 Tablets is a combination of two drugs (cyproterone acetate 2mg and ethinylestradiol 0.035mg) which is used in the treatment of women with androgen dependent skin conditions and may also be used as oral contraceptive in those women.

INDICATIONS

Clairette 2000/35 Tablets is indicated for use in women only for the treatment of (a) severe acne, refractory to prolonged oral antibiotic therapy; (b) moderately severe hirsutism.

Although Clairette 2000/35 Tablets also acts as an oral contraceptive, it is not recommended solely for contraception, but should be reserved for women requiring treatment for the androgen-dependent skin conditions described.

DOSE AND DOSE SCHEDULE

First treatment course:
One tablet daily for 21 days, starting on the first day of the menstrual cycle (the first day of menstruation counting as Day 1).

Subsequent courses:
Each subsequent course is started after 7 tablet-free days have followed the preceding course.

For full details refer to section 4.2 of the SPC.

TOXICOLOGY

No new toxicology data have been submitted or are required.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Cyproterone acetate: Following oral administration cyproterone acetate is completely absorbed in a wide dose range. The ingestion of Clairette 2000/35 Tablets effects a maximum serum level of 15ng cyproterone acetate/ml at 1.6 hours. Thereafter drug serum levels decrease in two disposition phases characterised by half-lives of 0.8 hours and 2.3 days. The total clearance of cyproterone acetate from serum was determined to be 3.6 ml/min/kg. Cyproterone acetate is metabolised by various pathways including hydroxylations and conjugations. The main metabolite in human plasma is the 15β-hydroxy derivative.

Some dose parts are excreted unchanged with the bile fluid. Most of the dose is excreted in form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days). Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 - 4.0% of total drug levels are present unbound. Because protein binding is non-specific changes in sex hormone binding globulin (SHBG) levels do not affect cyproterone acetate pharmacokinetics.

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake cyproterone acetate accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15ng/ml (day 1) to 21ng/ml and 24ng/ml at the end of the treatment cycles 1 and 3 respectively. The area under the concentration versus time profile increased 2.2 fold (end of cycle 1) and 2.4 fold (end of cycle 3). Steady state conditions were reached after about 16 days. During long term treatment cyproterone acetate accumulates over treatment cycles by a factor of 2.

The absolute bioavailability of cyproterone acetate is almost complete (88% of dose). The relative bioavailability of cyproterone acetate from co-cyprindiol was 109% when compared to an aqueous microcrystalline suspension.

Ethinylestradiol: Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of co-cyprindiol maximum drug serum levels of about 80pg/ml are reached at 1.7 hours. Thereafter ethinylestradiol plasma levels decrease in two phases characterised by half-lives of 1 - 2 hours and about 20 hours. For analytical reasons these parameters can only be calculated for higher dosages.

For ethinylestradiol an apparent volume of distribution of about 5 l/kg and a metabolic clearance rate from plasma of about 5 ml/min/kg were determined.

Ethinylestradiol is highly but non-specifically bound to serum albumin. 2% of the drug levels are present unbound. During absorption and first liver passage ethinylestradiol is metabolised resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.

According to the half-life of the terminal disposition phase from plasma and the daily ingestion steady state plasma levels are reached after 3 - 4 days and are higher by 30 - 40% as compared to a single dose. The relative bioavailability (reference: aqueous microcrystalline suspension) of ethinylestradiol was almost complete.

The systemic bioavailability of ethinylestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of vitamin C.

Ethinylestradiol induces the hepatic synthesis of SHBG and corticosteroid binding globulin (CBG) during continuous use. The extent of SHBG induction, however, is dependent upon the chemical structure and dose of the co-administered progestin. During treatment with co-cyprindiol SHBG concentrations in serum increased from about 100nmol/l to 300nmol/l and the serum concentrations of CBG were increased from about 50µg/ml to 95µg/ml.

Pharmacodynamics

Co-cyprindiol blocks androgen-receptors. It also reduces androgen synthesis both by a negative feedback effect on the hypothalamo-pituitary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Bioequivalence

A bioequivalence study to compare the test product, 2mg cyproterone acetate/0.035mg ethinylestradiol fixed-dose tablets and the reference product Diane 35® (2mg cyproterone acetate/0.035mg ethinylestradiol fixed-dose tablets, Schering France), was performed.

A qualified investigator was named.

The aim of this single centre, two-way, open, randomised, cross-over study was to evaluate the comparative bioavailability of the new oral tablet and of Diane 35® by measuring serum concentrations of cyproterone acetate and ethinylestradiol in 35 female postmenopausal healthy volunteers (aged 35-65 years) after single oral dose. It was conducted in compliance with GCP/ICH guidelines. 35 volunteers were recruited and 30 were analyzed for plasma levels and statistical analysis. 33 completed the study.

The volunteers received under fasting conditions the test product and reference product (Diane 35®) and there was a suitable wash-out period. The selection of doses in the study aimed to provide measurable levels of cyproterone acetate and ethinylestradiol. The values of C_{max} and AUC were examined using ANOVA.

The pharmacokinetic parameters of ethinylestradiol are illustrated in Table A and the parameters of cyproterone acetate in Table B.

Table A

Pharmacokinetic parameters of ethinylestradiol (n=30)			
	Test product	Diane 35®	90% CI
AUC_{0-t} (pg.h/ml)	2044.34 ± 761.49	2026.55 ± 612.80	92.21 – 104.66
$AUC_{0-\infty}$(pg.h/ml)	2274.67 ± 849.00	2229.15 ± 682.69	93.40 – 106.27
C_{max} (pg/ml)	169.23 ± 52.09	177.49 ± 58.72	91.94 – 100.29
$t_{½}$ (h)	16.07 ± 4.76	16.82 ± 5.39	
t_{max} (h)	2.0 ± 0.75	2.00 ± 0.50	

Table B

Pharmacokinetic parameters of cyproterone acetate (n=30)			
	Test product	Diane 35®	90% CI
AUC_{0-t} (pg.h/ml)	318206.1 ± 78626.9	327887.3 ± 85063.0	94.08 – 100.15
$AUC_{0-\infty}$ (pg.h/ml)	403149.9 ± 116224.5	428492.9 ± 132888.0	90.70 – 97.75
C_{max} (pg/ml)	27436.24 ± 5872.79	29942.10 ± 7268.07	86.23 – 97.63
$t_{½}$ (h)	103.56 ± 24.84	116.81 ± 38.68	
t_{max} (h)	2.00 ± 0.00	1.50 ± 0.50	

With regard to the target parameters for the evaluation of the bioequivalence for ethinylestradiol and cyproterone acetate, the 90% confidence interval lied within the acceptance range for bioequivalence (0.8-1.25), whether the C_{max}, the AUC_{0-t} and the $AUC_{0-\infty}$ are considered.

The study was clinically well tolerated.

Conclusion

Based on the results of the study, the new formulation and the reference Diane 35® formulation are bioequivalent with respect to the rate and extent of ethinylestradiol and cyproterone acetate absorption.

EFFICACY

The bio-equivalence study submitted has demonstrated that the applicant's product is bio-equivalent to the UK brand leader and therefore will have essentially the same clinical efficacy.

The clinical expert report provides a summary of the published literature on the cyproterone acetate/ethinylestradiol combination.

SAFETY

The bio-equivalence study submitted has demonstrated that the applicant's product is bio-equivalent to the UK brand leader and therefore will have essentially the same clinical safety profile.

The clinical expert report provides a summary of the published literature on the cyproterone acetate/ethinylestradiol combination.

EXPERT REPORT

A Clinical Expert Report has been submitted. Additionally, as the clinical expert is not medically qualified a supplementary statement has been submitted by an appropriately qualified medical professional.

Both experts review the relevant published information available on cyproterone acetate/ethinylestradiol combination and together with the results of the bioequivalence study they consider the product to be safe and efficacious.

SUMMARY OF PRODUCT CHARACTERISTICS

Satisfactory.

PATIENT INFORMATION LEAFLET

Satisfactory.

LABELLING

Satisfactory.

MARKETING AUTHORISATION APPLICATION (MAA) FORM

Satisfactory.

DISCUSSION

The use of orally administered cyproterone acetate/ethinylestradiol is well established in the treatment of severe acne and mild to moderate hirsutism and also as an oral contraceptive for women requiring treatment of these androgen-dependent skin conditions. The combination treatment has a well established safety profile.

The generic formulation, which is the subject of this application, has been shown in the comparative bioavailability study submitted to be bio-equivalent to the brand leader with confidence intervals within the required range for all C_{max} and AUC pharmacokinetic parameters. Therefore it is reasonable to conclude that the applicant's product will exhibit the same efficacy and safety profile.

CONCLUSIONS

The efficacy and safety of the product are satisfactory for the grant of a product licence.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Clairette 2000/35 Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Clairette 2000/35 Tablets and Diane 35 Tablets, which is qualitatively and quantitatively similar to the UK licensed Dianette Tablets (PL 00053/0190).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Dianette tablets.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with the combination of cyproterone acetate and ethinylestradiol is considered to have demonstrated the therapeutic value of the compounds. The risk-benefit assessment is therefore considered to be favourable.

CLAIRETTE 2000/35 TABLETS

(CYPROTERONE ACETATE / ETHINYLESTRADIOL) PL 14838/0004

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application for Clairette 2000/35 Tablets on 15 September 2003.
2	Following standard checks the MHRA informed the applicant that its application was considered valid on 24 November 2003
3	The MHRA's assessment of the submitted clinical data was completed on 23 January 2004
4	Further information was requested from the company on 28 January 2004 (clinical).
5	The MHRA's assessment of the submitted quality data was completed on 13 February 2004
6	Further information was requested from the company on 18 February 2004 (quality).
7	The applicant submitted its response to further information requests on 14 July 2004.
8	The applicant submitted a request relating to the product name on 19 October 2004.
9	Further information was requested from the company on 19 November 2004 (clinical) and 15 December 2004 (quality).
10	The applicant submitted its response to further information requests on 8 April 2005.
11	Further information was requested from the company on 26 August 2005.
12	The applicant submitted its response to additional information requests on 7 September 2005, 9 September 2005 and 30 November 2005.
13	Additional information on product particulars was requested from the company on 12 January 2006.
14	The applicant submitted its response to additional information request on 24 January 2006.
15	The MHRA completed its assessment of the updated product particulars on 24 January 2006.
16	The application was determined on 8 February 2006.

CLAIRETTE 2000/35 TABLETS

(CYPROTERONE ACETATE / ETHINYLESTRADIOL) PL 14838/0004

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Clairette 2000/35 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sugar-coated tablet contains 2mg cyproterone acetate and 35micrograms of ethinylestradiol.
For excipients, see section 6.1 (List of Excipients)

3. PHARMACEUTICAL FORM

Coated tablet
Clairette 2000/35 Tablets are white, biconvex, round tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Clairette 2000/35 Tablets are recommended for use in women only for the treatment of (a) severe acne, refractory to prolonged oral antibiotic therapy; (b) moderately severe hirsutism.
Although Clairette 2000/35 Tablets also act as an oral contraceptive, they should not be used in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent conditions described.

4.2. Posology and method of administration

Clairette 2000/35 Tablets inhibit ovulation and thereby prevent conception. Patients who are using Clairette 2000/35 Tablets should not therefore use an additional hormonal contraceptive, as this will expose the patient to an excessive dose of hormones and is not necessary for effective contraception.
First treatment course: One tablet daily for 21 days, starting on the first day of the menstrual cycle (the first day of menstruation counting as Day 1).
Subsequent courses: Each subsequent course is started after 7 tablet-free days have followed the preceding course.
When the contraceptive action of Clairette 2000/35 Tablets is also to be employed, it is essential that the above instructions be rigidly adhered to. Should bleeding fail to occur during the tablet-free interval, the possibility of pregnancy must be excluded before the next pack is started.
When changing from an oral contraceptive and relying on the contraceptive action of Clairette 2000/35 Tablets, follow the instructions given below:

Changing from 21-day combined oral contraceptives: The first Clairette 2000/35 tablet should be taken on the first day immediately after the end of the previous oral contraceptive course. Additional contraceptive precautions are not required.

Changing from a combined Every Day pill (28 day tablets):

The first Clairette 2000/35 tablet should be taken the day after taking the last active tablet from the Every Day Pill pack. Additional contraceptive precautions are not then required.

Changing from a progestogen-only pill (POP):

The first tablet of Clairette 2000/35 should be taken on the first day of bleeding, even if a POP has already been taken on that day. Additional contraceptive precautions are not then required. The remaining progestogen-only pills should be discarded.

Post-partum and post-abortum use:

After pregnancy, Clairette 2000/35 Tablets can be started 21 days after a vaginal delivery, provided that the patient is fully ambulant and there are no puerperal complications. Additional contraceptive precautions will be required for the first 7 days of pill taking. Since the first post-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets. Lactation is contra-indicated with Clairette 2000/35 Tablets. After a first-trimester abortion, Clairette 2000/35 Tablets may be started immediately in which case no additional contraceptive precautions are required.

Special circumstances requiring additional contraception

Incorrect administration: A single delayed tablet should be taken as soon as possible, and if this can be done within 12 hours of the correct time, contraceptive protection is maintained. With longer delays, additional contraception is needed. Only the most recently delayed tablet should be taken, earlier missed tablets being omitted, and additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used for the next 7 days, while the next 7 tablets are being taken. Additionally, therefore, if tablet(s) have been missed during the last 7 days of a pack, there should be no break before the next pack is started. In this situation, a withdrawal bleed should not be expected until the end of the second pack. Some breakthrough bleeding may occur on tablet taking days but this is not clinically significant. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack.

Gastro-intestinal upset: Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. Tablet-taking from the current pack should be continued. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastro-intestinal upset and for 7 days following the upset. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack. Other methods of contraception should be considered if the gastro-intestinal disorder is likely to be prolonged.

Complete remission of acne is to be expected in nearly all cases, often within a few months, but in particularly severe cases treatment for longer may be necessary before

the full benefit is seen. It is recommended that treatment be withdrawn 3 to 4 cycles after the indicated condition(s) has/have completely resolved and that Clairette 2000/35 Tablets are not continued solely to provide oral contraception. Repeat courses of Clairette 2000/35 Tablets may be given if the androgen-dependent condition(s) recur.

4.3. Contraindications

1. Pregnancy or lactation
2. Severe disturbances of liver function, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, previous or existing liver tumours.
3. Existing or previous arterial or venous thrombotic or embolic processes, and conditions which predispose to them e.g. disorders of the clotting processes , valvular heart disease and atrial fibrillation.
4. Sickle-cell anaemia.
5. Mammary or endometrial carcinoma, or a history of these conditions.
6. Severe diabetes mellitus with vascular changes.
7. Disorders of lipid metabolism.
8. History of herpes gestationis.
9. Deterioration of otosclerosis during pregnancy.
10. Undiagnosed abnormal vaginal bleeding.
11. Hypersensitivity to any of the components of Clairette 2000/35 Tablets.

4.4. Special warnings and precautions for use

Warnings: Like many other steroids, Clairette 2000/35 Tablets, when given in very high doses and for the majority of the animal's life-span, has been found to cause an increase in the incidence of tumours, including carcinoma, in the liver of rats. The relevance of this finding to humans is unknown.

In rare cases benign and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Clairette 2000/35 Tablets. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential diagnosis.

Clairette 2000/35 Tablets have many properties in common with combined oral contraceptives (COC), which must not be taken during treatment with Clairette 2000/35 Tablets. Statistical evidence suggests that users of combined oral contraceptives experience higher incidence of venous thromboembolism, arterial thrombosis, including cerebral and myocardial infarction, and subarachnoid haemorrhage, more often than non-users. Full recovery from such disorders does not always occur and in a few cases they are fatal. The frequency of these disorders in users of the modern low-dose pills is unknown, but they are thought to occur less often than with older pills.

Certain factors may entail some risk of thrombosis e.g. smoking, obesity, varicose veins, cardiovascular diseases, diabetes and migraine. The risk of arterial thrombosis

associated with combined oral contraceptives increases with age, and cigarette smoking aggravates this risk. In addition, if there is a family history of thromboembolic diseases at a young age (e.g. deep vein thrombosis, heart attack or stroke), disturbances of the coagulation system must be ruled out before Clairette 2000/35 Tablets are prescribed. The suitability of Clairette 2000/35 Tablets should be judged according to the severity of such conditions in individual cases, and should be discussed with the patient before taking it.

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer.

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer.

The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of Clairette 2000/35 Tablets (see *Precautions*).

Clairette 2000/35 therapy should be withdrawn immediately in the following circumstances:

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches.
2. Sudden disturbances of vision or hearing or other perceptual disorders.

3. First signs of thrombophlebitis or thromboembolic symptoms (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest.
4. Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin.
5. Onset of jaundice, hepatitis, itching of the whole body.
6. Increase in epileptic seizures.
7. Significant rise in blood pressure.
8. Onset of severe depression.
9. Severe upper abdominal pain or liver enlargement.
10. Clear worsening of conditions known to deteriorate during use of hormonal contraception or during pregnancy.
11. Pregnancy is a reason for stopping immediately because it has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but it is certain that if a risk exists at all, it is small.

Precautions:

Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast , abdominal and pelvic examination including cervical cytology.

<u>The following conditions require strict medical supervision</u> during medication with oral contraceptives. Deterioration or first appearance of any of these conditions may indicate that Clairette 2000/35 Tablets should be discontinued:
Diabetes mellitus, or a tendency towards diabetes mellitus (e.g. unexplained glycosuria), hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, disturbed liver function, Sydenham's chorea, renal dysfunction, family history of clotting disorders, obesity, family history of breast cancer and patient history of benign breast disease, history of clinical depression, systemic lupus erythematosus, uterine fibroids, an intolerance to contact lenses, migraine, gall-stones, cardiovascular diseases, chloasma, asthma, or any disease that is prone to worsen during pregnancy.

It should be borne in mind that the use of ultraviolet lamps, for the treatment of acne, or prolonged exposure to sunlight, increases the risk of the deterioration of chloasma.
Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of Clairette 2000/35 Tablets, especially when these conditions existed prior to use. Women should be informed of this possibility.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction

Hepatic enzyme inducers such as barbiturates, primidone, phenobarbitone, phenytoin, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the contraceptive efficacy of Clairette 2000/35 Tablets. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used. The use of antibiotics may also reduce the contraceptive efficacy of Clairette 2000/35 Tablets, possibly by altering the intestinal flora.

Women receiving short courses of enzyme inducers and broad spectrum antibiotics should take additional, non-hormonal (except rhythm or temperature method) contraceptive precautions during the time of concurrent medication and for 7 days afterwards. If these 7 days overrun the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

The possibility cannot be ruled out that oral tetracyclines, if used in conjunction with Clairette 2000/35 Tablets may reduce contraceptive efficacy, although it has not been shown. When drugs of these classes are being taken it is, therefore, advisable to use additional non-hormonal methods of contraception (except the rhythm or temperature methods) since an extremely high degree of protection must be provided when Clairette 2000/35 Tablets are being taken. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment stops, even if only a short course was administered.

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

The herbal remedy St John's wort (Hypericum perforatum) should not be taken concomitantly with Clairette 2000/35 Tablets as this could potentially lead to a loss of contraceptive effect.

4.6. Pregnancy and lactation

Contra-indicated.

Animal studies have revealed that feminisation of male foetuses may occur if cyproterone acetate is administered during the phase of embryogenesis at which differentiation of the external genitalia occurs. Although the results of these tests are not necessarily relevant to man, the possibility must be considered that administration of Clairette 2000/35 Tablets to women after the 45th day of pregnancy could cause feminisation of male foetuses. It follows from this that pregnancy is an absolute contra-indication for treatment with Clairette 2000/35 Tablets, and must be excluded before initiation of such treatment.

4.7. Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

There is an increased risk of venous thromboembolism for all women who use Clairette 2000/35 Tablets. For more information see section 4.4

In rare cases, headaches, gastric upsets, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, depressive moods can occur.

In predisposed women, use of Clairette 2000/35 Tablets can sometimes cause chloasma which is exacerbated by exposure to sunlight. Such women should avoid prolonged exposure to sunlight.

Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

Menstrual changes:

1. Reduction of menstrual flow: This is not abnormal and it is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

2. Missed menstruation: Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is unlikely. Should bleeding fail to occur during the tablet-free interval the possibility of pregnancy must be excluded before the next pack is started.

Intermenstrual bleeding: "Spotting" or heavier "breakthrough bleeding" sometimes occur during tablet taking, especially in the first few cycles, and normally cease spontaneously. Clairette 2000/35 Tablets should therefore, be continued even if irregular bleeding occurs. If irregular bleeding is persistent, appropriate diagnostic measures to exclude an organic cause are indicated and may include curettage. This also applies in the case of spotting which occurs at regular intervals in several consecutive cycles or which occurs for the first time after long use of Clairette 2000/35 Tablets.

Effect on blood chemistry: The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

Refer to Section 4.4. "Special warnings and special precautions for use" for additional information.

4.9. Overdose

There is no specific antidote. Treatment of overdosage should therefore be symptomatic.

Overdose may cause nausea, vomiting and, in females, withdrawal bleeding.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Clairette 2000/35 blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitiary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Although Clairette 2000/35 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.

5.2. Pharmacokinetic properties

Cyproterone acetate: Following oral administration cyproterone acetate is completely absorbed in a wide dose range. The ingestion of Clairette 2000/35 Tablets effects a maximum serum level of 15ng cyproterone acetate/ml at 1.6 hours. Thereafter drug serum levels decrease in two disposition phases characterised by half-lives of 0.8 hours and 2.3 days. The total clearance of cyproterone acetate from serum was determined to be 3.6 ml/min/kg. Cyproterone acetate is metabolised by various pathways including hydroxylations and conjugations. The main metabolite in human plasma is the 15β-hydroxy derivative.

Some dose parts are excreted unchanged with the bile fluid. Most of the dose is excreted in form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days). Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 - 4.0% of total drug levels are present unbound. Because protein binding is non-specific changes in sex hormone binding globulin (SHBG) levels do not affect cyproterone acetate pharmacokinetics.

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake cyproterone acetate accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15ng/ml (day 1) to 21ng/ml and 24ng/ml at the end of the treatment cycles 1 and 3 respectively. The area under the concentration versus time profile increased 2.2 fold (end of cycle 1) and 2.4 fold (end of cycle 3). Steady state conditions were reached after about 16 days. During long term treatment cyproterone acetate accumulates over treatment cycles by a factor of 2.

The absolute bioavailability of cyproterone acetate is almost complete (88% of dose). The relative bioavailability of cyproterone acetate from co-cyprindiol was 109% when compared to an aqueous microcrystalline suspension.

Ethinyloestradiol: Orally administered ethinyloestradiol is rapidly and completely absorbed. Following ingestion of co-cyprindiol maximum drug serum levels of about 80pg/ml are reached at 1.7 hours. Thereafter ethinyloestradiol plasma levels decrease in two phases characterised by half-lives of 1 - 2 hours and about 20 hours. For analytical reasons these parameters can only be calculated for higher dosages.

For ethinyloestradiol an apparent volume of distribution of about 5 l/kg and a metabolic clearance rate from plasma of about 5 ml/min/kg were determined.

Ethinyloestradiol is highly but non-specifically bound to serum albumin. 2% of the drug levels are present unbound. During absorption and first liver passage ethinyloestradiol is metabolised resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinyloestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day.

According to the half-life of the terminal disposition phase from plasma and the daily ingestion steady state plasma levels are reached after 3 - 4 days and are higher by 30 - 40% as compared to a single dose. The relative bioavailability (reference: aqueous microcrystalline suspension) of ethinyloestradiol was almost complete.

The systemic bioavailability of ethinyloestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of vitamin C.

Ethinyloestradiol induces the hepatic synthesis of SHBG and corticosteroid binding globulin (CBG) during continuous use. The extent of SHBG induction, however, is dependent upon the chemical structure and dose of the co-administered progestin. During treatment with co-cyprindiol SHBG concentrations in serum increased from about 100nmol/l to 300nmol/l and the serum concentrations of CBG were increased from about 50µg/ml to 95µg/ml.

5.3. Preclinical safety data

There are no pre-clinical safety data which could be of relevance to the prescriber and which are not already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate
Maize starch
Povidone K 25
Magnesium stearate
Talc
Sucrose
Calcium carbonate
Marcrogol 6000

Titanium dioxide (E171)
Povidone K 90
Glycerol 85%
Wax (montan glycol)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

No special storage precautions. Store in the original package.

6.5. Nature and contents of container

Packs of blister strips (aluminium foil/PVC) containing 21 or 63 tablets

6.6. Instruction for use and handling (and disposal)

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Harefield Pharma Associates Limited
Elite House
Hillfarm Industrial Estate
Leavesden
Watford
Hertfordshire
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 14838/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/02/2006

10 DATE OF REVISION OF THE TEXT

08/02/2006

Patient Information Leaflet

Clairette® 2000/35 tablets

CYPROTERONE ACETATE AND ETHINYLESTRADIOL

FOR ORAL USE

PATIENT INFORMATION LEAFLET

PLEASE READ THIS CAREFULLY BEFORE TAKING YOUR MEDICINE

It contains all the information you should need to know. If you have any further questions or are not sure about anything, ask your doctor or pharmacist. Please keep this leaflet in a safe place, you may wish to read it again.

• About your medicine

Your medicine is called Clairette 2000/35 Tablets. Each sugar-coated tablet contains two active ingredients, 2 mg of the anti-androgen, cyproterone acetate, and 35 micrograms of the oestrogen, ethinylestradiol, in a round, white, unmarked tablet.

Your medicine also contains the following other ingredients:
Lactose, maize starch, povidone, talc, magnesium stearate, sucrose, Macrogol 6000, calcium carbonate, glycerol 85%, montan glycol wax and titanium dioxide (E171).

Packs of 21 and 63 tablets are available.

Your medicine is a combination of an oestrogen (female hormone) and an anti-androgen. Cyproterone acetate belongs to a group of medicines called anti-androgens. Ethinylestradiol belongs to a group of medicines called oestrogens.

This product is manufactured by Haupt Pharma GmbH, Schleebruggenkamp 15, Munster, D-48159, Germany. The Product Licence holder is: Harefield Pharma Associates, Elite House, Hill Farm Industrial Estate, Leavesden, Watford, Herts, WD25 7SA.

• How does your medicine work and what is it used for ?

Your doctor has chosen this medicine as a suitable treatment for your skin. Although it is used for treating the skin, it is also an effective contraceptive. This means that when prescribing this medicine, your doctor has to deal with all the things that would apply to an ordinary oral contraceptive. While you are taking this medicine you should not take any other oral contraceptive pill.

Your body makes male sex hormones (androgens) as well as female sex hormones (oestrogens). Your ovaries have to make androgens so that they can be changed into oestrogens. Androgens stimulate the skin to grow but can also cause very greasy skin. This can lead to blockage of the grease-glands, which can then become infected and inflamed causing acne spots. Androgens may also cause more growth of hair on the face and body.

Your medicine works by blocking the action of androgens. Your medicine is used, in women only, to treat severe acne which has not improved after long term treatment with antibiotics, or to treat excessive hair on the face or body.

• Contraception with Clairette 2000/35 Tablets

As with ordinary oral contraceptives, your medicine prevents the release of eggs (ova). It also makes the mucus in the neck of the womb thick, so that sperm cannot get through, and makes the lining of the womb unsuitable for an egg to grow on. It prevents pregnancy as well as any ordinary combined contraceptive pill. Therefore, you do not need to use another contraceptive method to prevent pregnancy while taking this medicine; **there are some exceptions to this rule (please read under "What to do if you forget to take a pill and are relying on Clairette 2000/35 Tablets for contraceptive cover", "Stomach upsets" and "Taking other medicines").**

Your medicine is for the treatment of certain skin conditions (see above) and although the tablets also act as a contraceptive, they should not be used *only* for contraception after your skin problems have cleared up. Treatment with your medicine should be stopped by your doctor, 3 to 4 menstrual periods *after* your skin problems have cleared up.

• Before you take your medicine

You must not take Clairette 2000/35 Tablets if your answer to any of the following questions is YES:

- Are you pregnant, or do you think you may be pregnant, or are you breast-feeding?
- Have you ever had an allergic reaction to Clairette 2000/35 Tablets, cyproterone acetate, ethinylestradiol or any of the other ingredients in this medicine (allergic reactions include itching, rash, wheezing or shortness of breath)?
- Do you (or any member of your close family, e.g. parent, brother, sister) have, or have ever had, any blood clots in the legs, lungs, eyes or anywhere else?
- Have you (or any member of your close family, e.g. parent, brother, sister) had a heart attack, other heart disease, stroke or any medical condition, which makes you more at risk of developing blood clots?
- Do you suffer from abnormal red blood cells (e.g. sickle cell anaemia)?
- Do you suffer from disorders of blood fat (lipid) metabolism?
- Have you ever had or do you suffer from, cancer of the breast or of the lining of the womb?
- Have you suffered from long or short-term liver disease, or certain types of jaundice

If any of these conditions get worse or you have them for the first time this may be a sign that you should stop taking this medicine.

When you stop taking this medicine, it may take some time for your regular periods to return.

You should tell your doctor if you are taking any other medicines whether prescribed for you or bought without prescription.

Ultraviolet lamps (sunbeds) and prolonged sunbathing should be avoided if you are taking your medicine as their use increases the chance of chloasma, a patchy discoloration of the skin.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

• Taking other medicines

Some medicines may stop Clairette 2000/35 Tablets working properly as a contraceptive. If you are taking any other medicine while you are relying on Clairette 2000/35 Tablets for contraception, be sure to tell your doctor. Your doctor can tell you whether you should use extra contraceptive precautions and for how long.

Medicines, which can sometimes stop Clairette 2000/35 Tablets from working properly are antibiotics (such as ampicillin and rifampicin); griseofulvin (which is used to treat fungal infections); phenylbutazone (which is used to treat some types of joint diseases); phenytoin, primidone, phenobarbitone and some other medicines used in people with epilepsy, and carbamazepine (which can be used to treat epilepsy or other illnesses).

If you are relying on Clairette 2000/35 Tablets for contraception and you are taking any of these medicines you will need to use an extra contraceptive method (condoms or cap plus spermicide) while you are taking the other medicine and for 7 days after you stop taking it. If your present pack ends before these 7 days, start the next pack the next day without a break. If you run two packs together you may not have a period until the end of two packs, but this is not harmful.

If you do not have a period after the second pack, you must talk to your doctor before you start the next pack.

If your doctor prescribes oral antibiotics as well as this medicine for the treatment of your acne, you must tell your doctor if you want to rely on this medicine for contraception. Medicines applied to the skin, including antibiotics, will not affect the contraceptive reliability of Clairette 2000/35 Tablets. However, if you are taking an antibiotic called rifampicin, and you are relying on Clairette 2000/35 Tablets for contraception, you will need to use another method of contraception as well as Clairette 2000/35 Tablets. You should do this while you are taking the rifampicin and for 4 weeks after you stop.

If you are a diabetic your doctor may alter the dose of medicine required to treat your diabetes.

The herbal remedy St John's wort (Hypericum perforatum) should not be taken at the same time as Clairette 2000/35 Tablets. If you already take a St John's wort preparation, stop taking the St John's wort and mention it to your doctor at your next visit.

If you are in doubt, check with your doctor or pharmacist.

• Stomach upsets:

Being sick or having very bad diarrhoea may stop this medicine from working properly. If this happens and you are relying on this medicine for contraception, carry on taking it as usual, and also use another method of contraception (condoms or cap plus spermicide), until 7 days after you have recovered from the stomach upset.

If you finish your pack before these 7 days, start the next pack the next day without a break. If you run two packs together you may not have a period until the end of two packs, but this is not harmful. If you do not have a period after the second pack, you must talk to your doctor before starting the next pack. If your stomach upset continues for some time, consult your doctor who may consider another form of contraception.

• Warnings:

Pregnancy:
If you think you might be pregnant, stop taking Clairette 2000/35 Tablets immediately and consult your doctor. Use another method of contraception, such as a condom until you see the doctor.

Clairette 2000/35 Tablets have many properties similar to "combined" contraceptive pills

- Do you suffer from disorders of blood fat (lipid) metabolism?
- Have you ever had or do you suffer from, cancer of the breast or of the lining of the womb?
- Have you suffered from long or short-term liver disease, or certain types of jaundice (Dubin-Johnson or Rotor syndrome)?
- Do you have abnormal bleeding from your vagina of unknown cause?
- Do you suffer from severe diabetes with changes to the blood vessels?
- Do you suffer from, or have you ever had, liver tumours?

Do not take this medicine if you have had any of these conditions when you were pregnant:
- Itching of your whole body (pruritis of pregnancy)
- The rash known as herpes gestationis.
- Worsening of inherited deafness (otosderosis).
- Yellowing of the skin (jaundice)

Before you start taking your medicine, your doctor will ask you about your medical history by asking you some questions about yourself and will ask these questions when you visit the surgery again. Your doctor will also take your blood pressure and may check your breasts, abdomen and pelvis. You may also need to have a cervical smear test. Your doctor will also make sure you are not pregnant.

Tell your doctor if anyone in your family has had any illness caused by blood clots, or a heart attack, or a stroke at a young age.

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If you have, or have had, any of the following conditions, your doctor will check you carefully while you are taking your medicine:
- Severe depression
- Varicose veins
- Diabetes or a tendency towards diabetes
- High blood pressure
- Fits (epilepsy)
- Otosclerosis (an inherited form of deafness).
- Multiple sclerosis
- Porphyria
- Calcium deficiency with cramps (tetany)
- Sydenham's chorea (a movement disorder)
- Breast problems
- Problems of the heart and blood vessels
- Kidney problems
- Disturbed liver function
- You are overweight (obese)
- An intolerance to contact lenses
- Systemic lupus erythematosus (inflammation of connective tissue)
- Asthma
- Uterine fibroids (benign tumour of the womb)
- Gallstones
- Migraine
- Brown patches on the face and body (chloasma)
- Any illness that is prone to worsen during pregnancy
- Inflamed veins (phlebitis)
- A family history of breast cancer
- A family history of illness caused by blood clots, a heart attack or stroke at a young age

you see the doctor.

Clairette 2000/35 Tablets have many properties similar to "combined" contraceptive pills (containing two hormones). The following statements which refer to combined oral contraceptive pills, also apply to Clairette 2000/35 Tablets:

The risk of developing various disorders of the circulation of the blood may be slightly greater in women who take the combined pill than in those who do not. This can lead to, for example, deep vein thrombosis (blood clot in the leg), strokes (blood clots and haemorrhages from the blood vessels in the brain), heart attacks or pulmonary embolism (blood clots blocking the arteries of the lungs). In extremely rare cases, blood clots can form in other places such as the liver, gut, kidney or eye.

People do not always fully recover from these disorders, and very rarely they are fatal. Studies suggest that these disorders occur less often with modern low-dose oral contraceptives than with older pills.

A blood clot can develop whether or not you are taking the pill. It can also develop if you become pregnant. The risk of a blood clot is higher in people who take the pill than in people who don't.

Certain conditions increase the risk of thrombosis. They include:

- Smoking (with heavier smoking and increasing age, the risk increases).
  Stop smoking if you are using the pill, especially if you are over 35 years of age.
- Age (the risk of having a heart attack or stroke increases as you get older)
- Obesity (if you are very overweight)
- Some diseases of the heart (valve or irregular rhythm disorders)and blood vessels - high blood pressure, or if you have a disorder of blood fat (lipid) metabolism, sickle cell disease, or some other very rare blood disorders
- Diabetes
- Migraine
- A major operation or period of immobilisation (e.g. you are in bed after an accident or operation or you have a plaster cast on a broken leg)
- If any members of your close family have suffered from thrombo-embolic diseases (e.g. deep vein thrombosis, stroke or heart attack) at a young age
- Varicose veins
- If you have recently given birth

If any of theses conditions apply to you, before you decide to take this medicine or while you are taking it you must discuss them with your doctor.

The risk of arterial thrombosis (e.g. heart attack and stroke) associated with the pill increases with age, and this risk is increased by cigarette smoking. For this reason, doctors discourage the use of combined pills by women in the older age group, especially those who also smoke. Signs and symptoms of blood clots are given in the 'side-effects' section under 'Reasons for stopping Clairette 2000/35 Tablets immediately'.

The pill does give a substantial degree of protection against cancers of the ovary and the lining of the womb. There may be an increased risk of cervical cancer in long term users of the pill.

Breast cancer: Every woman is at risk of breast cancer whether or not she takes the Pill. Breast cancer is rare under the age of 40 years, but the risk increases as a woman gets older. Breast cancer has been found slightly more often in women who take the Pill than in women of the same age who do not take the Pill. If women stop taking the Pill this reduces the risk so that 10 years after stopping the Pill, the risk of finding breast cancer is the same as for women who have never taken the Pill.

On rare occasions, the use of the pill has led to liver problems such as jaundice and benign liver tumours, and malignant liver tumours (cancer) in long term users. If you have pain in your tummy (abdomen) that does not soon clear up, tell your doctor. Also, if your skin becomes yellow (jaundice), you must tell your doctor.

Reasons for stopping Clairette 2000/35 Tablets immediately: if you experience any of the following take no further tablets and see your doctor immediately (in the meanfime use another method of contraception such as a condom):

- Migraine (if you haven't experienced migraine before) or if your migraine occurs more often than before
- unusually bad headaches or if you have headaches more often than before
- sudden changes to your eyesight, hearing, speech, and sense of smell, taste or touch.
- dizziness or fainting
- unusual pains in your leg or unusual swelling of your arms or legs, sharp pains in your chest or sudden shortness of breath, crushing pains or feelings of heaviness in your chest, coughing for no apparent reason, or if one side of your body suddenly becomes very weak or numb.
- your skin becomes yellow (jaundice), you develop hepatitis (inflammation of the liver) or your whole body starts itching.
- an increase in the number of fits (epileptic seizures).
- a large increase in blood pressure.
- severe depression.
- severe upper abdominal pains or unusual swelling of the abdomen.
- worsening of conditions which had got worse during a previous pregnancy or whilst taking the pill in the past.
- pregnancy.
- Surgery or being immobile (you must stop taking Clairette 2000/35 Tablets 6 weeks before a planned major operation, e.g. stomach surgery, if you are having any surgery to the legs, or medical treatment for varicose veins).

Also, if you are not mobile for a long time e.g. you are in bed after an accident or operation or you have a plaster cast on a broken leg. Your doctor will advise you when to start taking Clairette 2000/35 Tablets again.

Effect on blood tests: The use of this medicine may affect the results of certain laboratory tests. Always tell your doctor or the laboratory staff that you are using Clairette 2000/35 Tablets.

• How to take your medicine

Follow the doctor's instructions and check the directions in this leaflet, which should tell you how many tablets to take in one day. If it does not or you are not sure what to do, consult your doctor or pharmacist. Your medicine should be taken by mouth and swallowed whole with water.

If you are relying on this medicine for contraception, it is important that you follow these instructions carefully and read the section 'Contraception with Clairette 2000/35 Tablets':

• When to start

If you are new to Clairette 2000/35 Tablets or are starting it again after a break, take your first tablet on the first day of a menstrual period i.e. when you start to bleed. For other users, follow instructions for 'Changing from another type of oral contraceptive', 'Starting your medicine after having a baby' or 'Starting Clairette 2000/35 Tablets after miscarriage or an abortion'.

Start with a pill marked (on the foil blister strip) with the correct day of the week. For instance, if your period starts on a Tuesday, start with a pill marked 'Tues'.

• Taking your first pack of Clairette 2000/35 Tablets:

After taking your first pill, take one pill each day following the arrows on the foil strip as marked for each day of the week until you have finished all 21 pills in the pack. You should try to take the pill at the same time every day, for example, after breakfast. Swallow each pill whole, with water. By starting this way you will have contraceptive protection at once.

• Your seven pill-free days:

After you have taken all 21 tablets, you have 7 days when you take no tablets. A few days after you have taken your last pill from each pack, you will have a period. Your periods will be regular, probably lighter than before and almost always painless. The feelings that often make the last days before your period unpleasant (called pre-menstrual syndrome) usually disappear. You are very unlikely to become pregnant during the 7 day break from taking the pill, as long as you have taken your pills correctly, and start the next pack on time.

• Taking your next pack of Clairette 2000/35 Tablets:

Start taking your next pack of Clairette 2000/35 Tablets after 7 pill-free days. Each new pack will begin on the same day of the week as the one before, it is easy to remember when to start again. You should start taking your next pack after 7 days, even if you are still bleeding.

• Changing from any other type of oral contraceptive:

While you are taking your medicine

• When can you expect to see an improvement in your skin?

You will first notice that your skin becomes much less greasy, then after about three months, you should see a definite improvement in acne. If you are taking this medicine to treat excessive hair growth on your body or face, you may have to wait a few months, possibly longer, to see a definite improvement.

• How long can you take your medicine?

Your doctor will stop treating you with this medicine when your skin is completely clear, or the amount of body and facial hair growth has decreased. **Treatment with Clairette 2000/35 Tablets should be stopped by your doctor, 3 to 4 menstrual periods *after* your skin problems have cleared up.**
You will be able to have further courses of treatment, for as long as necessary, if the problem keeps returning.

• What to do if you miss a period

If you have no bleeding in the 7 day break, whether you have missed tablets or not tell your doctor as soon as possible and do not start another pack until your doctor tells you to. In the meantime, do not have sex unless you use condoms or a cap plus spermicide.

• What if you have bleeding between periods?

A small number of women may have a little breakthrough bleeding or spotting while taking this medicine, especially during the first few months. Normally this bleeding is nothing to worry about and will stop in a day or two. Keep taking the pills as usual and the problem should disappear after the first few packs. If the bleeding keeps on returning, is annoying or long-lasting, talk to your doctor. Also, if you start to have breakthrough bleeding for the first time after being on this medicine for a long time, you should see your doctor. Unexpected bleeding may also be a sign of irregular pill-taking, so try to take your pill at the same time everyday.

• What to do if you forget to take a pill and are relying on Clairette 2000/35 Tablets for contraceptive cover:

If you are more than twelve hours late in taking a pill, or have missed more than one pill:
Contraceptive protection may be lower, so you must use extra protection. Follow the instructions for the "7 day" rule.

"7-day" rule:
- Take the most recent 'late' pill and continue to take your next pills at normal times

And
- Use an extra contraceptive method (condoms or cap plus spermicide) for the next 7 days.

And
- If tablet(s) have been missed during the last 7 days of a pack, there should be no break before the next pack is started. This means taking a pill every day during your normal 7 pill-free days. You will not have a period until you have finished the next pack, but this is not harmful. You may see some bleeding on pill-taking days, but do not worry. If no bleeding occurs in the 7-day break, see under the sub-heading 'What to do if you miss a period' (above).

• If one pill is 12 hours late or less:

Contraceptive protection should not be affected if you take the late pill at once, and keep taking your next pills at the usual time. If you are not sure what to do, ask your doctor or pharmacist.

• What should you do if you lose a pill?

If you lose a pill, the easiest thing to do is take the last pill of your pack in place of the lost pill. Then take all of the pills on their proper days. Your cycle will be one day shorter than normal, but contraceptive protection is not affected. After your 7 pill-free days, you will have a new starting day, one day earlier than before. Should you lose a pack of pills halfway through, ask your doctor or pharmacist what to do.

• What to do if you want to have a baby?

The bleeding you have after each pack (including the last pack) is not a true period. Your doctor relies on the date of your last true period before you get pregnant to tell you when your baby will be born. So, if you stop taking Clairette 2000/35 Tablets to have a baby, use another method of contraception until you have had a true period. However it will not be harmful if you become pregnant straight away.

• What to do if you take too many tablets

If you take too many tablets, it may cause nausea, vomiting or withdrawal bleeding. Consult your doctor who will advise you what action to take, if necessary. Take some of the tablets with you to show your doctor.

• Side Effects of your medicine

As with all medicines, Clairette 2000/35 Tablets can cause unwanted side effects in some patients.

Sometimes mild unwanted effects can occur in the first few months after starting your medicine. These include:
- Bleeding and spotting between your periods which can sometimes occur

• Changing from any other type of oral contraceptive:

21 day pill
If you are taking a 21-day contraceptive pill, finish that pack and then start taking Clairette 2000/35 Tablets the next day. Do not leave a gap between packs. Start with a pill marked with the correct day of the week. Then follow the instruction as described earlier (see 'Taking your first pack of Clairette 2000/35 Tablets'). **By starting in this way you will have contraceptive protection at once.** You may not have a period until the end of the pack, but this is not harmful. You may have some bleeding on pill-taking days, but do not worry.

• Every Day (ED) combined pill (28 day pill):

The first Clairette 2000/35 Tablet should be taken the day after taking the last active tablet from the Every Day Pill pack. You will not then need additional contraceptive protection. If you are not sure which tablets are the active ones, ask your doctor or pharmacist. The first tablet of Clairette 2000/35 Tablets is taken the next day, which means that you do not leave a gap between packs. Start with a pill marked with the correct day of the week. Return to your pharmacist any remaining inactive tablets from your old Every Day pack. Then follow the instructions as before (see 'Taking your first pack of Clairette 2000/35 Tablets'). **By starting in this way you will have contraceptive protection at once.** You may not have a period until the end of the first pack, but this is not harmful. You may have some bleeding on the pill-taking days, but do not worry.

•Mini pill (progestogen only pill):

The first tablet of Clairette 2000/35 Tablets should be taken on the first day of the period, even if you have already taken a mini pill on that day. Return any mini pills left in your old pack to your pharmacist. Start with a pill marked with the correct day of the week. Follow the instructions as before (see 'Taking your first pack of Clairette 2000/35 Tablets'). **By starting in this way you will have contraceptive protection at once.**

• Starting Clairette 2000/35 Tablets after having a baby:

If you have just had a baby, and providing you are mobilising and there are no other medical problems your doctor may advise you to start taking Clairette 2000/35 Tablets 21 days after delivery. You do not have to wait for a period. **You will need to use another method of contraception until you start your medicine and for the first 7 days pill taking.** Follow the instructions as before (see 'Taking your first pack of Clairette 2000/35 Tablets'). You must not breastfeed if you take Clairette 2000/35 Tablets.

• Starting Clairette 2000/35 Tablets after a miscarriage or an abortion

If you have just had a miscarriage or an abortion, your doctor may advise you to start using Clairette 2000/35 Tablets immediately. Follow the instructions as before (see 'Taking your first pack of Clairette 2000/35 Tablets').

Sometimes mild unwanted effects can occur in the first few months after starting your medicine. These include:
- Bleeding and spotting between your periods which can sometimes occur in the first few months, but this usually stops once your body has adjusted to your medicine. If it continues, becomes heavy, or starts again, contact your doctor.
- Headaches
- Feeling sick, being sick and stomach upsets
- Sore breasts
- Depressive moods, loss of interest in sex.
- Changes in weight.
- Chloasma (yellow / brown patches on the skin). This may happen even if you have been using your medicine for a number of months. Chloasma may be reduced by avoiding too much sunlight.
- Poor tolerance to contact lenses.

More serious reactions have sometimes been associated with contraceptive pills that contain oestrogen and progestogen, for example thrombosis (for formation of a clot in blood vessels) or liver disease. These are explained in the 'Warnings' section (above).

If you think that you have a serious adverse reaction to Clairette 2000/35 Tablets, stop taking your tablets and consult your doctor as soon as possible.

You should also see your doctor if you feel any other unusual or unexpected side effects not mentioned above during or after taking your medicine. He or she will have more information about your medicine and will tell you what to do.

This medicine is for YOUR use only. It can only be prescribed by a doctor. Never give it to anyone else. It may harm them even if their symptoms are the same as yours.
This leaflet does not contain the complete information about your medicine. If you have any further questions, or are not sure about anything, ask your doctor or pharmacist who has access to additional information.

KEEP YOUR MEDICINE IN A SAFE PLACE WHERE CHILDREN CANNOT SEE IT OR GET AT IT

No special storage precautions. Store in the original package.

Do not use these tablets if the expiry date has been passed.
Do not use these tablets if they appear to be damaged or appear to have deteriorated in any way.

Leaflet prepared: November 2005

Clairette® 2000/35 tablets
CYPROTERONE ACETATE AND ETHINYLESTRADIOL

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CLIENT	PRODUCT	
HAREFIELD	CLAIRETTE 2000/35 TABLETS	
MODIFIED ON	JOB	SIZE / mm
25.11.2005	LEAFLET (UK)	180 x 420
vista multimedia sa	VISTA MULTIMEDIA SA - 37 PH. DE SAUVAGE - 1219 GENEVA SWITZERLAND TEL. + 41 22 970 17 11 - FAX + 41 22 970 17 12 - VISTA@VISTAMULTIMEDIA.CH	

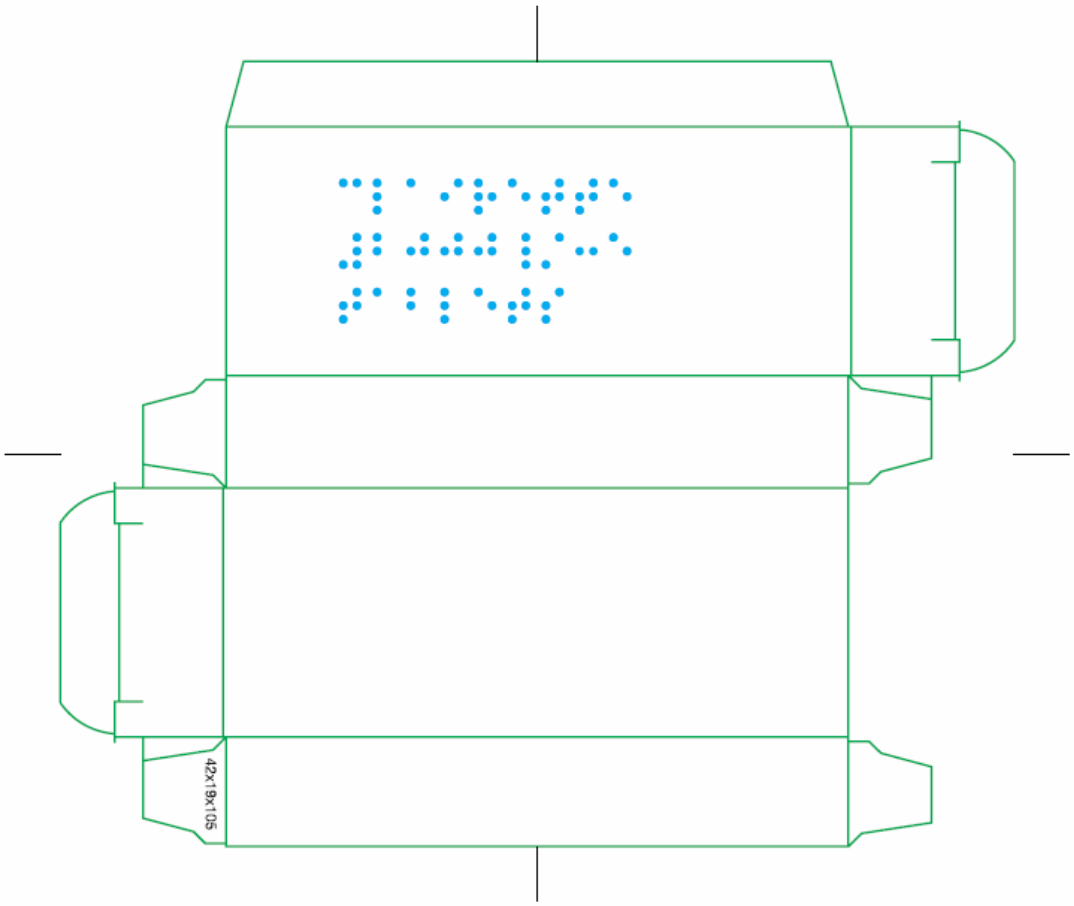
Labels/Packaging

21-tablet carton

63-tablet carton

Blister strip

Braille on packaging



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Braille: Clairette 2000/35 Tablets
Satz: Haupt Pharma MS/wdm