

**CYPROTERONE ACETATE 50MG TABLETS
(CYPROTERONE ACETATE)
PL 08137/0127**

**CYPROTERONE ACETATE 100MG TABLETS
(CYPROTERONE ACETATE)
PL 08137/0128**

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**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

**CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128**

LAY SUMMARY

The MHRA granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Cyproterone Acetate 50mg Tablets (PL08137/0127) and Cyproterone Acetate 100mg Tablets (PL 08137/0128) on 11th April 2006. This prescription only medicine (POM) can be taken by males to control an overactive sex-drive and to relieve the symptoms caused by a tumour of the prostate gland.

Cyproterone acetate tablets contain the active ingredient cyproterone acetate, which is an anti-androgen, which blocks the action of male sex hormones (androgens), released naturally in the body and reduces the production of androgens.

The clinical data presented to the MHRA, pre licensing, demonstrated that Cyproterone Acetate 50mg & 100mg Tablets are essentially similar or equivalent to the approved products Cyprostat 50mg and 100mg tablets. Cyproterone Acetate tablets can therefore be used interchangeably with Cyprostat tablets.

No new or unexpected safety concerns arose from these applications. It was, therefore, judged that the benefits of taking Cyproterone Tablets outweigh the risks. Hence Marketing Authorisations have been granted.

**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

**CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Cyproterone Acetate 50mg Tablets (PL 08137/0127) and Cyproterone Acetate 100mg Tablets (PL 08137/0128) to Neolab Limited on 11th April 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 10.1 [formerly article 10.1 (a)(iii)] of Directive 2001/83/EC, claiming essential similarity to the original products Cyprostat 50mg & 100mg Tablets.

The product contains the active ingredient Cyproterone Acetate and is indicated for the control of libido in severe hypersexuality and/or sexual deviation in adult males and for management of patients with prostatic cancer.

Cyproterone acetate is a progestational steroid with strong anti-androgen activities, and also reduces secretion of testosterone (and other androgens).

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

These are abridged applications for Marketing Authorisation in the UK submitted under Article 10.1 of Directive 2001/83 (as amended) for products claiming essential similarity to Cyprostat tablets 50mg (PL 00053/0133) and 100mg (PL 00053/0218). The licences were granted on the 15th February 1982 and the 5th July 1993 respectively, and are held by Schering Healthcare Limited. Cyprostat tablets 100mg were used as the medicinal product in the bioequivalence study.

The Cyprostat tablet 50mg licence is a copy of Androcur tablets 50mg (PL 00053/0023), also held by Schering Healthcare Limited, with different indications.

2. DRUG SUBSTANCE

2.1 General information

There is no certificate of suitability for the drug substance. However, an EDMF is available. The EDMF was received on the 13th November 2001, with an update listed on the 14th July 2003. A letter of access for these products has been provided.

2.2 Manufacture

2.2.1 Manufacturers

There are two sites listed for the manufacture of the active ingredient.

The Active Ingredient Manufacturer (AIM) has provided a statement of confirmation that the synthetic route, quality control, procedures and specifications for cyproterone acetate are identical for both manufacturing sites. The addition of the alternative site as a manufacturing site has previously been approved.

2.2.2 Manufacturing process

The starting ingredient is cyclised using standard techniques in the presence of suitable solvents to get crude cyproterone acetate. The crude product is extracted and purified.

2.2.3 Elucidation of structure and other characteristics

The structure has been demonstrated using IR absorption, mass spectrum, proton nuclear magnetic resonance, differential scanning calorimetry and x-ray diffraction.

Cyproterone acetate contains six chiral centres. Polymorphism is said not to exist based on available literature, this is also evident from DSC.

2.3 Control of drug substance

2.3.1 Specification

The AIMs specifications for cyproterone acetate have been supplied. These include the requirements of the European Pharmacopoeia. The specifications are taken from the manufacturer's certificate of analysis.

The finished product manufacturer will test cyproterone acetate to the European Pharmacopoeia monograph. Tests for particle size, residual solvents and tapped density will be taken from the active substance manufacturer.

The method used for the determination of residual solvents has been validated. The method is precise and accurate. The limits of detection and quantitation are acceptable.

Certificates of analysis have been included for batches produced at both manufacturing sites. These include the material used in the manufacture of the biobatch of finished product. All results are within specification.

2.3.2 Container closure system

The material is packed in virgin food grade double polyethylene bags enclosed in black polyethylene bags. Each of the polyethylene bags are sealed using a plastic fastener and a cellophane tape. The bagged material is kept in a fibre drum with a lid and free galvanized ring, bottom and top made of plywood.

2.3.3 Stability

Stability data has been presented for batches manufactured at each site.

Data has been supplied for tests conducted under long-term and accelerated conditions. The batches have been assessed on assay, degradation products, IR identification, specific optical rotation and loss on drying. All batches remain in specification at the relevant time points.

The finished product manufacturer has an acceptable retest date for cyproterone acetate of 2 years.

3. DRUG PRODUCT

3.1 Composition

The qualitative composition of the tablets is summarised in table 1. The Cyproterone acetate 50mg tablets are white circular uncoated tablets with a break line on one side and plain on the other side. The Cyproterone 100mg tablets are white, capsule shaped uncoated tablets with a break line on one side and 'CPA100' on the other side.

The tablets are packed in PVC/PVdC – aluminium foil blisters.

Table 1

Name of Ingredients	Reference
Active	
Cyproterone acetate	Ph Eur
Excipients	
Lactose monohydrate	Ph Eur
Maize starch	Ph Eur
Povidone (K-30)	Ph Eur
Pregelatinised maize starch	Ph Eur
Magnesium stearate	Ph Eur
Colloidal anhydrous silica	Ph Eur

The quantity of cyproterone acetate dispensed is adjusted according to assay.

The 100mg tablet is a direct scale up of the 50mg tablet, with the tablets generated being sufficiently different in appearance.

3.2 Pharmaceutical Development

3.2.1 Formulation development

The formulas chosen are similar to that of the cross-reference products. Only the Cyprostat tablets 50mg contain anhydrous colloidal silica, whereas both strengths of Cyproterone acetate tablets contain anhydrous colloidal silica. This information has been taken from the relevant SPC for each of the products.

Compatibility of cyproterone acetate with the excipients has been assumed, as they are present in the existing licensed product.

The function of each of the excipients has been stated and all are commonly used in the preparation of tablets by wet granulation. The concentrations used are within commonly utilised levels.

The formula for the 100mg was produced by directly scaling up the formulation ratios of the 50mg tablet.

3.3 Manufacture

3.3.1 Manufacturer(s)

An MCA inspection letter dated April 2002 has been provided, stating that the original manufacturing site has been inspected (tablets and nasal sprays) and can be named as a manufacturing site.

3.3.2 Batch formula

The batch formulas for preparation of Cyproterone acetate 50mg tablets and Cyproterone acetate 100mg tablets have been provided.

The maximum batch sizes for the respected strengths have been provided. The actual amount of cyproterone acetate used is corrected depending on the assay, modifying if necessary the amount of lactose monohydrate. The water used in the process is stated as being purified water Ph. Eur..

3.3.3 Manufacturing process and process controls

A flow diagram detailing the manufacturing process has been provided. A written summary of the process has been included.

3.3.4 In-process controls

Appropriate in-process controls are in place.

Adequate details on the sample size and frequency of samples taken for in-process control testing have also been supplied.

3.3.5 Control of critical steps and intermediates

3.3.6 Process validation or evaluation

Validation has been performed on three production scale batches (one batch of the Cyproterone acetate 50mg tablets and two batches of Cyproterone acetate 100mg tablets) manufactured according to the proposed manufacturing process. All the batches were put on to stability and one of the 100mg tablet batches was used as the biobatch.

The tablets produced for the 50mg batch and the two 100mg batches are compliant with the relevant specifications.

It has been confirmed that the first two batches of the 50mg tablet and first batch of the 100mg tablet produced at the commercial batch sizes are to undergo the same validation protocol for the compression part of the manufacturing process and deviations will be reported.

3.4 Control of excipients

3.4.1 Specification

Lactose monohydrate, maize starch, povidone, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate and purified water have monographs in the Ph. Eur..

A certificate of analysis from each of the respective raw material manufacturers have been supplied for each of the excipients. Certificates of analysis have been supplied from the finished product manufacturer.

The magnesium stearate has been supplied with a certificate of suitability in respect of TSE/BSE requirements. Appropriate documentation has been provided by the supplier of the lactose.

The finished product manufacturer will test the first three batches of the excipients and then a minimum of an identification test, when supplied with a certificate of analysis detailing compliance to the European Pharmacopoeia monograph. If there is no certificate of analysis the materials will be tested to the full monograph.

The purified water is produced on site from potable water. The potable water and purified water are sampled on a weekly basis. In-process controls are also conducted..

3.5 Control of drug product

3.5.1 Specification

The finished product specifications for the tablets have been provided and comply with the requirements in the BP.

The limits proposed have been suitably justified.

3.5.2 Analytical procedures

Where relevant the test methods used are those described in the Ph. Eur. The identification and assay is performed using a HPLC method. A very similar HPLC method is used to analyse the related substances. Both HPLC methods are based on the methods in the BP monograph for Cyproterone tablets. Identification is also determined by IR.

3.5.3 Validation

The HPLC method for assay has been validated. The method has precision and accuracy. Specificity and linearity have also been shown.

The HPLC method for related substances has been validated. Detection limit and quantitation limits are acceptable. Specificity has been shown in relation to mobile phase, placebo and stressed samples.

The UV method for dissolution has been validated. Linearity has been demonstrated over a suitable range. The method has precision. Specificity has been shown in relation to mobile phase and placebo. Robustness has been shown.

Validation data in relation to the microbiology methods used to assess the quality of the tablets has been provided.

3.5.4 Batch analyses

Batch analyses of the batches manufactured during validation of the process are provided. Also included is the pilot scale batch produced using the original manufacturing method.

These batches have also been placed on stability and one of the 100mg batches was used in the bioequivalence.

The batches presented use active substance from two different batches.

3.6 Container closure system

The blister packaging used is composed of PVC film, coated with PVdC, and aluminium foil.

The active substance needs to be protected from light and the SPC states the storage conditions 'keep container in the outer carton'. There is no specific requirement in the BP monograph for the finished product to protect it from light, however the stressed samples demonstrated photo-instability. The warning to keep the blisters in the outer carton with an explanation why in the PIL has been included which is acceptable.

Certificates of analysis are supplied from the finished product manufacturer and the manufacturer of the packaging. Certificates of conformity for the packaging components have also been supplied.

3.7 Stability

Two batches of each strength have been placed on stability.

The tablets were checked on description, average weight, friability, hardness, disintegration, water content, dissolution, assay, related substances and microbiology. Microbiological testing was performed initially and at the last interval.

The data provided demonstrates that both strengths are stable products. The data generated shows evidence of an increase in impurities, an increase in moisture and a decrease in assay in the 100mg tablets with an apparent lack of mass balance, though these remain in specification. There is also a decrease in dissolution with time under accelerated conditions.

The decrease in assay of the 100mg tablets and lack of mass balance, seen for separate batches under accelerated and long-term conditions has been put down to moisture pick up, evident by an increase in weight in addition to the increase in moisture content. To reduce this effect the storage condition of do not store above 25°C has been included. The decrease in dissolution seen under accelerated conditions has also been explained by moisture pick-up. The dissolution profiles with individual tablet data demonstrate reasonable uniformity. The parameters remain in specification, additional controls for storage have been applied and the dissolution method will be superseded by the BP2004 methodology which is considered acceptable.

The applicant is proposing a shelf life of 24 months, with the intention of extending this time when more data becomes available. The proposed storage conditions are 'do not store above 25°C', 'keep blisters in the outer carton' and 'store in the original package'. On the data presented this is acceptable.

Confirmation has been supplied that the first two batches of the 50mg tablet and the first batch of the 100mg tablet produced at the commercial batch size are to be placed on stability using the same stability protocol as currently being used.

3.8 Other information

3.8.1 Bioanalytical methods

Cyproterone acetate and the metabolite 15 β -OH-cyproterone are extracted by solid phase extraction, evaporation to dryness and reconstitution. Quantification is by HPLC equipped with a UV detection system. Validation of the method has been performed. The method is linear over a range relevant for determination of cyproterone and 15 β -OH-cyproterone in the plasma samples. It has been demonstrated that the method is selective for Cyproterone and 15 β -OH-cyproterone, however the assay has not been tested for interference from other drugs. The limits of quantitation are at suitable levels. The method has also been shown to be precise and accurate.

3.8.2 Bioequivalence

The bioequivalence study was a comparative, randomised, single-dose, 2-way crossover study. Comparing the Cyproterone acetate 100mg tablets with Cyprostat 100mg tablets from Schering, UK, in healthy adults at a dose of 100mg. Twenty four subjects were enrolled in the study. Data were analysed for twenty two, due to one withdrawing prior to the start of the study and the other withdrawing on doctors advice after phase one for reasons stated as being not related to the study medication.

One 100mg tablet was given for each of the medications. Samples were taken predose and at specified intervals post-dose.

Bioequivalence was determined using the 90% confidence interval of the relative mean AUC 0-t, AUC ∞ and Cmax of the test to reference formulation which should be 80% to 125%.

The batch of Cyproterone acetate 100mg tablets is at least 1/10 of the proposed maximum batch size.

The 90% confidence intervals for the log-transformed pharmacokinetic parameters were

	Cyproterone	15 β -OH-cyproterone
AUC 0-t	92.0% - 100.4%	91.1% - 102.7%
AUC ∞	93.1% - 100.6%	90.9% - 102.2%
Cmax	96.1% - 120.1%	92.8% - 112.9%

The confidence intervals derived are within the 80% to 125% acceptance range of the Notes for Guidance on Bioavailability and Bioequivalence. Cyproterone acetate 100mg tablets were therefore considered to be bioequivalent to Cyprostat 100mg tablets following administration under fasting conditions of a 100mg dose.

3.8.3 Essential similarity

The dissolution profiles of the Cyproterone acetate 100mg tablets are comparable to Cyprostat 100mg tablets. This has been conducted only on the batches used in the bioequivalence study. Dissolution of the development batches is comparable to the batches used in the bioequivalence study.

The related impurities for the 100mg development batches at the end of shelf-life have been compared to the 100mg reference product almost at expiry using the pharmacopoeia method. Though the impurities in the development batches were much higher than the reference product they were still well within specification and in compliance with the guidelines on impurities. This is considered to be acceptable.

4. PRODUCT LITERATURE

4.1 SPC

From a Pharmaceutical prospective the SPC is compliant with the guidelines and representative of the quality data presented.

4.2 PIL

From a Pharmaceutical prospective the PIL is compliant with the guidelines and representative of the quality data presented.

4.3 LABEL

From a Pharmaceutical prospective the label is compliant with the guidelines and representative of the quality data presented.

5. ADMINISTRATIVE

5.1 MAA form

The MAA form has been completed as required and is representative of the quality data presented.

5.2 Quality Overall Summary

An independent pharmaceutical consultant has completed the summary. The report is a summary of the module.

6. CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

These are national abridged standard applications for marketing authorisations for Cyproterone Acetate 50 mg Tablets, PL 08137/0127 and Cyproterone Acetate 100mg Tablets (PL 08137/0128). The applicant claims essential similarity to Cyprostat Tablets 50 mg (PL 00053/0133) and Cyprostat Tablets 100 mg (PL 00053/0218), licensed to Schering Healthcare Ltd and first granted 15th February 1982 and 5th July 1993, respectively. The application is made under article 10.1 [formerly article 10.1(a)(iii)] of EC Directive 2001/83.

2. BACKGROUND

In the UK, Schering Healthcare Ltd first obtained a marketing authorisation for 50 mg Cyproterone Acetate tablets in 1974 under the brand name Androcur[®] (PL 00053/0023) for the control of libido in severe hypersexuality and sexual deviation in adults. Subsequently, marketing authorisation under the name of Cyprostat[®] (PL 00053/0133) was granted to Schering for 50 mg cyproterone acetate tablets in 1982 for the treatment of patients with prostate cancer. Both medicinal products are considered identical. In other member states Schering only market cyproterone acetate 50 mg tablets under the single name of Androcur[®] with both severe hypersexuality and sexual deviation and prostate cancer as the recommended indications.

Prostatic carcinoma is generally dependent on androgens. Cyproterone acetate is a steroid with strong anti-androgen activities, and in addition cyproterone acetate exerts a negative feedback on the hypothalamic receptors.

3. INDICATIONS

50mg only:

For control of libido in severe hypersexuality and/or sexual deviation adult male.

50mg and 100mg:

For the management of patients with prostatic cancer (1) to suppress “flare” with initial LHRH analogue therapy, (2) In long-term palliative treatment where LHRH analogues or surgery are contraindicated", not tolerated, or oral therapy is preferred, and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy.

4. DOSE & DOSE SCHEDULE

For oral administration only.

Control of libido in severe hypersexuality and/or sexual deviation.

Adults and the elderly:

The usual dose is 50 mg twice daily. The daily dose should be divided and taken after the morning and evening meals.

Children (under 18 years old):

Not recommended.

The management of patients with prostatic cancer

Adults and the elderly:

To suppress "flare" with initial LHRH Analogue therapy: 300mg/day which may be reduced to 200mg if the higher dose is not tolerated.

In long term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or when oral therapy is preferred: 200 - 300 mg/day.

For the above two indications the dosage should be divided into 2-3 doses per day and taken after meals.

In the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy: 50 mg starting dose with upward titration if necessary within the range 50-150mg/day. For this indication the dosage should be divided into 1-3 doses per day and taken after meals

Children:

Not recommended.

5. TOXICOLOGY

No new toxicology data have been submitted or are required.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACOKINETICS

Following oral administration of tablets, cyproterone acetate is quickly and completely absorbed over a wide dosage range. The absolute bioavailability of cyproterone acetate is almost complete.

Cyproterone acetate is metabolised by hydrolysis to free cyproterone, and then to 15 β -hydroxycyproterone. Excretion occurs via the bile (70%) and urine (30%). Only small amounts of unchanged drug are found in the bile, most is excreted in the form of metabolites.

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 – 4% of total drug levels are present unbound. Because protein binding is non-

specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

6.2 PHARMACODYNAMICS

Prostatic carcinoma and its metastases are generally dependent on androgens. Cyproterone acetate is a progestational steroid with strong anti-androgen activities, and in addition cyproterone acetate exerts a negative feedback on the hypothalamic receptors; therefore suppressing gonadotrophin release, and hence secretion of testosterone (and other androgens) is reduced.

6.3 BIOEQUIVALENCE

A bioequivalence study has been conducted to compare the rates and extent of absorption of cyproterone from the proposed new formulation and the reference product, Cyprostat®. The study was conducted according to GCP.

Study design

This was a comparative, randomised, single dose, two-way crossover bioavailability study of cyproterone 100 mg tablets versus Cyprostat® 100 mg tablets (Schering Health Care Ltd, UK) in 24 healthy volunteers aged 18 to 51 years. Of the 24 subjects, most were of European origin but 1 was African, 1 Australian, 1 Malaysian/Chinese and 1 from Hong Kong.

Subjects received a single oral dose of 1 tablet 100 mg cyproterone from the test and reference formulation in a fasting state, on two separate occasions. A wash out period of 14 days was allowed between doses. No comparative pharmacokinetic studies have been performed with the 50 mg strength as this is a dose proportional formulation to the 100 mg.

Blood samples were taken just before dosing and then at specified intervals after dosing.

22 subjects successfully completed the study. 1 subject withdrew from the study prior to phase one induction and was not replaced. Another subject withdrew from the study for reasons not related to study medication.

Results

The plasma samples from this study were analysed using a validated HPLC method with UV detection. Pharmacokinetic parameters of cyproterone and its major metabolite 15 β -OH-Cyproterone, C_{max} , AUC_{0-t} and $AUC_{0-\infty}$, were calculated (statistical analysis using ANOVA) and are summarised below.

Cyproterone	Geometric Mean Values (\pm S.D.)		Ratio	90% Confidence Interval%
	Test	Reference		
C_{max} (ng/ml)	230.3 (\pm 69.2)	214.4 (\pm 68.9)	107.44%	96.1-120.1*

AUC_{0-t} (ng.ml/h)	5165.1 (±1339.7)	5372.2 (±1306.6)	96.15%	92.0-100.4*
AUC_{0-inf} (ng.ml/h)	5633.0 (±1326.8)	5821.7 (±1351.3)	96.76%	93.1-100.6*
Mean Values				
T_{max} (h)	2.66	3.32		
Half-life (h)	46.94	47.13		

*Log transformed values

15β-OH-Cyproterone	Geometric Mean Values (± S.D.)		Ratio	90% Confidence Interval%
	Test	Reference		
C_{max} (ng/ml)	157.7 (±44.0)	154.0 (±35.3)	102.38%	92.8-112.9*
AUC_{0-t} (ng.ml/h)	8845.2 (±2943.5)	9144.6 (±2455.1)	96.73%	91.1-102.7*
AUC_{0-inf} (ng.ml/h)	9404.2 (±3166.8)	9760.5 (±2672.2)	96.35%	90.9-102.2*
Mean Values				
T_{max} (h)	4.21	5.08		
Half-life (h)	49.91	52.73		

*Log transformed values

There were 8 subjects who complained of a total of 12 adverse events. No subject was required to be withdrawn due to adverse events. It is of note that of the events reported only mild headache was felt to be related to cyproterone administration.

Conclusion

The ratios of the main criteria for efficacy (the peak plasma concentrations and the areas under the concentration curves) lie within the normal limits for acceptance of 80-125%. It can, therefore, be concluded that the test product has similar *in vivo* bioavailability to the reference product.

7. EFFICACY

No new efficacy data have been submitted or are required for this application. The bio-equivalence study submitted has demonstrated that the applicant product is bio-equivalent to the reference product and therefore will have essentially the same clinical efficacy.

8. SAFETY

The bio-equivalence study submitted has demonstrated that the applicant product is bio-equivalent to the reference product and therefore will have essentially the same clinical safety. The safety results from the bioequivalence study were satisfactory. Otherwise, no other new safety data have been submitted or are required for this application.

9. EXPERT REPORT

A clinical overview written by a Consultant Pharmaceutical Physician and Medical Practitioner has been submitted. The expert has the appropriate qualifications and the report is satisfactory.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The SPCs are satisfactory.

11. PATIENT INFORMATION LEAFLET

The PILs supplied are satisfactory.

12. LABELLING

Carton mock-ups for all pack sizes have been submitted and are satisfactory.

13. MARKETING AUTHORISATION FORM

The MAA form is satisfactory.

14. DISCUSSION

These are national applications for marketing authorisations for Cyproterone Acetate 50 mg Tablets and Cyproterone Acetate 100mg Tablets submitted as essential similarity to Cyprostat Tablets 50 mg and 100mg licensed to Schering Healthcare Ltd in 1982 and 1993, respectively.

In the UK, Schering Healthcare Ltd first obtained a marketing authorisation for 50 mg Cyproterone Acetate tablets in 1974 under the brand name Androcur[®] for the control of libido in severe hypersexuality and sexual deviation in adults. Subsequently, marketing authorisation under the name of Cyprostat[®] was granted to Schering for 50 mg cyproterone acetate tablets in 1982 for the treatment of patients with prostate cancer. Both medicinal products are identical. Cyproterone Acetate 50mg Tablets are intended for both indications, whereas Cyproterone Acetate 100mg Tablets are indicated only in the treatment of patients with prostatic cancer.

A bioequivalence study has been conducted to compare the rates and extent of absorption of cyproterone from the proposed new formulation and the reference product, Cyprostat[®]. The ratios of the main criteria for efficacy lie within the normal limits for acceptance of 80-125%. It can, therefore, be concluded that the test product has similar *in vivo* bioavailability to the reference product.

No new preclinical or efficacy data have been submitted or are required for this application. The safety results from the bioequivalence study were satisfactory. The SPC, PIL and labelling are satisfactory.

15. CONCLUSIONS

The efficacy and safety of Cyproterone Acetate Tablets are satisfactory for the grant of product licences.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Cyproterone Acetate 50mg & 100mg 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 Cyproterone Acetate Tablets and Cyprostat tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Cyprostat 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 products and the innovator products are interchangeable. Clinical experience with cyproterone acetate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

**CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128**

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 27/01/2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 27/02/2004.
3	Following assessment of the application the MHRA requested further information relating to the medical dossier on 02/07/2004 and 03/03/2006.
4	The applicant responded to the MHRA's requests, providing further information relating to the medical dossier on 04/08/2004, 19/10/2004 and 27/03/2006.
5	Following assessment of the application the MHRA requested further information relating to the quality dossier on 21/10/2004 and 13/06/2005.
6	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 24/03/2005 and 18/08/2005.
7	The application was determined on 11/04/2006.

**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

**CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128**

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate 50 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg cyproterone acetate.

Excipient: Lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet.

White, circular shaped tablet with a central breakline on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For control of libido in severe hypersexuality and/or sexual deviation adult male.

For the management of patients with prostatic cancer (1) to suppress “flare” with initial LHRH analogue therapy, (2) In long-term palliative treatment where LHRH analogues or surgery are contraindicated", not tolerated, or oral therapy is preferred, and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy.

4.2. Posology and method of administration

For oral administration only.

Control of libido in severe hypersexuality and/or sexual deviation.

Adults and the elderly:

The usual dose is 50 mg twice daily. The daily dose should be divided and taken after the morning and evening meals.

Children:

Its use is not recommended in children and adolescents (under 18 years).

The management of patients with prostatic cancer

Adults and the elderly:

To suppress "flare" with initial LHRH Analogue therapy: 300mg/day which may be reduced to 200mg if the higher dose is not tolerated.

In long term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or when oral therapy is preferred: 200 - 300 mg/day.

For the above two indications the dosage should be divided into 2-3 doses per day and taken after meals.

In the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy: 50 mg starting dose with upward titration if necessary within the range 50-150mg/day. For this indication the dosage should be divided into 1-3 doses per day and taken after meals

Children:

Its use is not recommended in children and adolescents (under 18 years).

4.3. Contraindications

Use in patients known to be hypersensitive to cyproterone acetate or to any of the ingredients of the Cyproterone Acetate Tablets.

Additional contraindications for patients being treated for hypersexuality / sexual deviation

Cyproterone acetate is contraindicated for use in patients with liver diseases; malignant tumours (other than prostatic cancer); wasting diseases (because of transient catabolic action); a history of or existing thrombosis or embolism; severe diabetes with vascular changes; sickle-cell anaemia; severe chronic depression. Cyproterone acetate should not be given to youths under the age of 18 or to those whose bone maturation and testicular maturation is incomplete.

4.4. Special warnings and precautions for use

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 - 300 mg/day cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the

hepatotoxicity can be attributed to another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

As with other sex steroids, benign and malignant liver changes have been reported in isolated cases.

Very rarely liver tumours, leading in isolated cases to life-threatening intra-abdominal haemorrhage, have been observed after the use of sex steroids, to which class cyproterone acetate belongs. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, hepatic tumour should be considered in the differential diagnosis and, if necessary, cyproterone acetate should be withdrawn.

Thromboembolism: patients with a history of thrombosis may be at risk of recurrence of the disease during cyproterone acetate therapy. In patients with a history of thromboembolic disorders or suffering from sickle-cell anaemia or severe diabetes with vascular changes, the risk: benefit ratio must be considered carefully in each individual case before cyproterone acetate is prescribed.

In very rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate; a casual relationship seems however questionable.

Chronic depression: It has been found that some patients with severe chronic depression deteriorate during cyproterone acetate therapy.

Breathlessness: Shortness of breath may occur. Possibly due to the known stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, but it is not considered that treatment is required.

Adrenocortical function: During treatment adrenocortical function should be monitored, since suppression has been observed.

Diabetes: Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.

Haemoglobin: Hypochromic anaemia has been found rarely during long term treatment, and blood counts before and at regular intervals during treatment are advisable.

Nitrogen balance: a negative nitrogen balance is usual at the start of treatment, but usually does not persist.

Spermatogenesis: A spermatogram should be recorded before starting treatment in patients of procreative age, as a guard against attribution of pre-existing infertility to cyproterone acetate at a later stage.

It should be noted that decline in spermatogenesis is slow and cyproterone acetate should not be regarded as a male contraceptive.

Doctors are advised that fully informed consent of the patient to cyproterone acetate treatment is obtained and can be verified.

The tablets also contain lactose (see 6.1.). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment. The requirement for oral antidiabetic treatment or insulin can change.

Alcohol appears to reduce the effect of cyproterone acetate, which is of no value in chronic alcoholics.

4.6. Pregnancy and lactation

Not applicable. Cyproterone acetate is not indicated for use in women.

4.7. Effects on ability to drive and use machines

Fatigue and lassitude are common in the first few weeks of therapy but usually become much less marked from the third month.

The marked lassitude and asthenia necessitate special care when driving or operating machinery.

4.8. Undesirable effects

Inhibition of spermatogenesis: The sperm count and the volume of ejaculate is reduced. Infertility is usual, and there may be azoospermia after eight weeks. There is usually slight atrophy of the seminiferous tubules. Follow up examinations have shown these changes to be reversible, spermatogenesis usually reverting to its previous state about three to five months after stopping treatment or in some users up to 20 months. That spermatogenesis can recover even after very long treatment is uncertain. There is evidence that abnormal sperms, which might give rise to malformed embryos, are produced during treatment.

Tiredness: Fatigue and lassitude are common in the first few weeks of treatment but become less from the third month.

Breathlessness: A sensation of shortness of breath may occur under high-dose treatment with cyproterone acetate, owing to the known stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, and is not considered to require treatment.

Gynaecomastia: Some patients develop transient or perhaps in some cases permanent enlargement of the mammary glands. In rare cases galactorrhoea and tender benign nodules have been reported. Symptoms mostly subside after discontinuation of treatment or reduction of dosage, but this should be weighed against the risk to the tumour of using inadequate doses.

Bodyweight: During long-term treatment, changes in body weight have been reported. Both increases and decreases have been seen.

Other changes that have been reported include reduction of sebum production and consequently improvement of existing acne vulgaris, transient patchy loss and reduced growth of body hair, increased growth of scalp hair, lightening of hair colour and female type of pubic hair growth.

Rarely, cases of osteoporosis have been reported.

Hypersensitivity reactions and rashes may occur in rare cases.

See also sections 4.4 and 4.7.

4.9. Overdose

There have been no reports of ill effects from overdosage, which is, therefore, generally unnecessary to treat. There are no special antidotes and treatment should be symptomatic. If overdosage is discovered within 2 to 3 hours and is so large that treatment seems desirable, gastric lavage can be safely used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: G03H AO1

Prostatic carcinoma and its metastases are generally dependent on androgens. Cyproterone acetate is a progestational steroid with strong anti-androgen activities, and in addition cyproterone acetate exerts a negative feedback on the hypothalamic receptors; therefore suppressing gonadotrophin release, and hence secretion of testosterone (and other androgens) is reduced.

5.2. Pharmacokinetic properties

Following oral administration of tablets, cyproterone acetate is quickly and completely absorbed over a wide dosage range. The absolute bioavailability of cyproterone acetate is almost complete. The maximal plasma levels after a single dose are achieved after about 3 hours. After oral administration of 100 mg daily the steady state plasma concentration is 260 ± 50 ng/ml. The mean plasma half life is about 2 days.

Cyproterone acetate is metabolised by hydrolysis to free cyproterone, and then to 15 β -hydroxycyproterone. Excretion occurs via the bile (70%) and urine (30%). Only small amounts of unchanged drug are found in the bile, most is excreted in the form of metabolites.

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 – 4% of total drug levels are present unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

5.3. Preclinical safety data

Experimental investigations produced corticoid-like effects on the adrenal glands in rats and dogs following higher dosages, which could indicate similar effects in humans at the highest given dose (300 mg/day).

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One *in vivo* consequence of cyproterone acetate treatment was the increased incidence of focal, possibly preneoplastic, liver lesions in which cellular enzymes were altered in female rats. The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate, colloidal anhydrous silica.

6.2. Incompatibilities

None known.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in original package. Keep blisters in the outer carton.

6.5. Nature and contents of container

PVC/PVdC – aluminium foil blisters containing 56 tablets.

6.6. Instruction for use and handling (and disposal)

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Neolab Ltd
57 High Street
Odiham
Hants
RG29 1LF

8. MARKETING AUTHORISATION NUMBER

PL 08137/0127

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/04/2006

10. DATE OF REVISION OF THE TEXT

11/04/2006

CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cyproterone Acetate 100 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg cyproterone acetate.

Excipient: Lactose monohydrate.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet.

White, capsule shaped tablet with a breakline on one side and 'CPA 100' marked on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the management of patients with prostatic cancer (1) to suppress "flare" with initial LHRH analogue therapy, (2) in long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred, and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy.

4.2. Posology and method of administration

For oral administration only.

Adults and the elderly:

To suppress "flare" with initial LHRH Analogue therapy: 300mg/day which may be reduced to 200mg if the higher dose is not tolerated.

In long term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or when oral therapy is preferred: 200 - 300 mg/day.

For the above two indications the dosage should be divided into 2-3 doses per day and taken after meals.

In the treatment of hot flushes in patients under treatment with LHRH analogues or who have had an orchidectomy: 50 mg starting dose with upward titration if necessary within the range 50-150mg/day. For this indication the dosage should be divided into 1-3 doses per day and taken after meals

Children:

Its use is not recommended in children and adolescents (under 18 years).

4.3. Contraindications

Use in patients known to be hypersensitive to cyproterone acetate or to any of the ingredients of the Cyproterone Acetate Tablets.

4.4. Special warnings and precautions for use

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 200 - 300 mg/day cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be attributed to another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.

As with other sex steroids, benign and malignant liver changes have been reported in isolated cases.

Very rarely liver tumours, leading in isolated cases to life-threatening intra-abdominal haemorrhage, have been observed after the use of sex steroids, to which class cyproterone acetate belongs. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, hepatic tumour should be considered in the differential diagnosis and, if necessary, cyproterone acetate should be withdrawn.

Thromboembolism: patients with a history of thrombosis may be at risk of recurrence of the disease during cyproterone acetate therapy. In patients with a history of thromboembolic disorders or suffering from sickle-cell anaemia or severe diabetes with vascular changes, the risk: benefit ratio must be considered carefully in each individual case before cyproterone acetate is prescribed.

In very rare cases, the occurrence of thromboembolic events has been reported in temporal association with the use of cyproterone acetate; a casual relationship seems however questionable.

Chronic depression: It has been found that some patients with severe chronic depression deteriorate during cyproterone acetate therapy.

Breathlessness: Shortness of breath may occur. Possibly due to the known stimulatory effect of progesterone and synthetic progestogens on breathing, which is accompanied by hypocapnia and compensatory alkalosis, but it is not considered that treatment is required.

Adrenocortical function: During treatment adrenocortical function should be monitored, since suppression has been observed.

Diabetes: Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.

Haemoglobin: Hypochromic anaemia has been found rarely during long term treatment, and blood counts before and at regular intervals during treatment are advisable.

Nitrogen balance: a negative nitrogen balance is usual at the start of treatment, but usually does not persist.

The tablets also contain lactose (see 6.1). Patients with rare hereditary problems of galactose intolerance, the Lapp deficiency or glucose-galactose malabsorption should not take this medicine.

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

Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment. The requirement for oral antidiabetic treatment or insulin can change.

Alcohol appears to reduce the effect of cyproterone acetate.

4.6. Pregnancy and lactation

Not applicable. Cyproterone Acetate Tablets are not indicated for use in women.

4.7. Effects on ability to drive and use machines

Fatigue and lassitude are common in the first few weeks of therapy but usually become much less marked from the third month.

The marked lassitude and asthenia necessitate special care when driving or operating machinery.

4.8. Undesirable effects

Inhibition of spermatogenesis. The sperm count and the volume of ejaculate is reduced. Infertility is usual, and there may be azoospermia after eight weeks. There is usually slight atrophy of the seminiferous tubules. Follow up examinations have shown these changes to be reversible, spermatogenesis usually reverting to its previous state about three to five months after stopping treatment or in some users up to 20 months. That spermatogenesis can recover even after very long treatment is uncertain. There is evidence that abnormal sperms, which might give rise to malformed embryos, are produced during treatment.

Tiredness: Fatigue and lassitude are common in the first few weeks of treatment but become less from the third month.

Gynaecomastia: Some patients develop transient or perhaps in some cases permanent enlargement of the mammary glands. In rare cases galactorrhoea and tender benign nodules have been reported. Symptoms mostly subside after discontinuation of treatment or reduction of dosage, but this should be weighed against the risk to the tumour of using inadequate doses.

Bodyweight: During long-term treatment, changes in body weight have been reported. Both increases and decreases have been seen.

Other changes that have been reported include reduction of sebum production and consequently improvement of existing acne vulgaris, transient patchy loss and reduced growth of body hair, increased growth of scalp hair, lightening of hair colour and female type of pubic hair growth.

Rarely, cases of osteoporosis have been reported.

Hypersensitivity reactions and rashes may occur in rare cases.

See also sections 4.4 and 4.7.

4.9. Overdose

There have been no reports of ill effects from overdosage, therefore, generally it is unnecessary to treat. There are no special antidotes and treatment should be symptomatic. If overdosage is discovered within 2 to 3 hours and is so large that treatment seems desirable, gastric lavage can be safely used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code: G03H AO1

Prostatic carcinoma and its metastases are generally dependent on androgens. Cyproterone acetate is a progestational steroid with strong anti-androgen activities, and in addition cyproterone acetate exerts a negative feedback on the hypothalamic receptors; therefore suppressing gonadotrophin release, and hence secretion of testosterone (and other androgens) is reduced.

5.2. Pharmacokinetic properties

Following oral administration of tablets, cyproterone acetate is quickly and completely absorbed over a wide dosage range. The absolute bioavailability of cyproterone acetate is almost complete. The maximal plasma levels after a single dose are achieved after about 3 hours. After oral administration of 100 mg daily the steady state plasma concentration is 260 ± 50 ng/ml. The mean plasma half life is about 2 days.

Cyproterone acetate is metabolised by hydrolysis to free cyproterone, and then to 15 β -hydroxycyproterone. Excretion occurs via the bile (70%) and urine (30%). Only small amounts of unchanged drug are found in the bile, most is excreted in the form of metabolites.

Cyproterone acetate is almost exclusively bound to plasma albumin. About 3.5 – 4% of total drug levels are present unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

5.3. Preclinical safety data

Experimental investigations produced corticoid-like effects on the adrenal glands in rats and dogs following higher dosages, which could indicate similar effects in humans at the highest given dose (300 mg/day).

Recognised first-line tests of genotoxicity gave negative results when conducted with cyproterone acetate. However, further tests showed that cyproterone acetate was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats and monkeys and also in freshly isolated human hepatocytes. This DNA-adduct formation occurred at exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. One *in vivo* consequence of cyproterone acetate treatment was the increased incidence of focal, possibly preneoplastic, liver lesions in which cellular enzymes were altered in female rats. The clinical relevance of these findings is presently uncertain. Clinical experience to date would not support an increased incidence of hepatic tumours in man.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate, colloidal anhydrous silica.

6.2. Incompatibilities

None known.

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in original package. Keep blisters in the outer carton.

6.5. Nature and contents of container

PVC/PVdC – aluminium foil blisters containing 84 tablets.

6.6. Instruction for use and handling (and disposal)

No specific recommendations applicable

7. MARKETING AUTHORISATION HOLDER

Neolab Ltd
57 High Street
Odiham
Hants
RG29 1LF

8. MARKETING AUTHORISATION NUMBER

PL 08127/0128

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/04/2006




10 DATE OF REVISION OF THE TEXT

11/04/2006

CYPROTERONE ACETATE 50MG TABLETS

PL 08137/0127

PRODUCT INFORMATION LEAFLET



PATIENT INFORMATION LEAFLET
CYPROTERONE ACETATE 50 mg TABLETS

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

What is in your medicine?

Each tablet contains 50 mg of the active ingredient Cyproterone Acetate.

Other ingredients: Lactose monohydrate, maize starch, pre-gelatinised maize starch, povidone, magnesium stearate, colloidal anhydrous silica.

Cyproterone Acetate 50 mg Tablets are available in blister packs of 56 tablets. Your pharmacist will dispense the number of tablets prescribed by your doctor.

Cyproterone Acetate belongs to a group of medicines called anti-androgens. Cyproterone Acetate blocks the actions of male sex hormones (androgens) which are released naturally in your body. It also reduces the production of androgens.

The Marketing Authorisation Holder and manufacturer responsible for batch release is Neolab Ltd, 57 High Street, Odlingham, Hants, RG29 1LF.

Uses

Since Cyproterone Acetate reduces the amount of androgens in the body it can be taken by males to control an overactive sex drive.

It has been shown that the growth of tumours of the prostate gland may be dependent on male hormones. Since Cyproterone Acetate blocks the action of androgens and reduces the amount of androgens produced by the body, it can be used to help relieve the symptoms of a tumour of the prostate gland.

Before taking your medicine

Do not take this medicine if:

- You have had any allergic reaction (wheezing, runny nose, skin rashes) to Cyproterone Acetate, other similar medicines (steroids), or any of the other ingredients in the tablets.
- You have been told by your doctor that you have an intolerance to some sugars (e.g. lactose).

If you are being treated for an overactive sex drive you should also not take this medicine if:

- You have liver disease.
- You know you have or have had tumours, other than in your prostate gland.
- You suffer from any illness making you thin, weak or tired.
- You have a history of blood clots (heart attack, stroke, thrombosis or embolism).
- You suffer from diabetes.
- You suffer from a condition called sickle-cell anaemia (abnormalities of the red blood cells).
- You suffer from, or have suffered from depression.
- You are under 18 years of age.

Tell your doctor immediately as the medicine may not be suitable for you.

Also tell your doctor before you start taking this medicine if:

- You drink alcohol, even if it is not regularly.
- You are planning a family.

You should **NOT** drink alcohol whilst taking Cyproterone Acetate Tablets.

If you are diabetic and your doctor decides that you can still take Cyproterone Acetate Tablets, your doctor may alter the dose of medicine (oral antidiabetic treatments or insulin) required to treat your diabetes.

It is likely that your doctor will arrange regular blood tests whilst you are taking Cyproterone Acetate Tablets.

Your doctor may also check your sperm count before and during treatment. Whilst Cyproterone Acetate Tablets may reduce the production of sperm, the medicine must not be used instead of contraception.

This medicine may make you feel tired or weak. If you are affected, do not drive or work machinery.

Please read the back of this leaflet.

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Taking your medicine

Follow your doctor's directions about when and how to take your medicine and look at the dispensing label on the carton. Your pharmacist will help you if you are not sure.

Cyproterone Acetate Tablets should be swallowed whole with a glass of water after meals. Do not reduce the dose or stop the treatment unless your doctor tells you to.

For adults including the elderly, the normal dose to control an overactive sex drive is 50 mg (one tablet) twice a day. Your doctor can only prescribe this medicine for an overactive sex drive once he has explained what the tablets will do and you have agreed to take them.

For adults including the elderly, the normal doses to help relieve the symptoms of a prostatic tumour are as follows:

- To reduce the possible worsening ('flare up') of a prostatic tumour, which can happen during the first few weeks of starting other treatments for prostatic tumours (e.g. Buserelin Injection), the usual daily dosage is 300 mg (two tablets three times a day). Sometimes the daily dosage may be reduced by your doctor to 200 mg (two tablets twice a day).
- In long term treatment where other treatments or surgery are unsuitable, the usual daily dosage is 200 mg to 300 mg (two tablets two or three times a day).
- To treat hot flushes caused by other treatments for prostatic tumours or following surgical removal of the testicles, the usual daily dosage is 50 mg to 150 mg (one tablet once or three times a day).

What to do in case of an overdose

If you take too much of your medicine contact your doctor immediately.

What to do if you forget to take a dose

If you forget to take a dose take it as soon as you remember. If it is almost time for your next dose though, do not double the dose, just carry on as before.

Possible side-effects

As with other medicines you may experience side effects.

If any of the following happen, STOP taking the medicine and tell your doctor IMMEDIATELY or go to the casualty department at your nearest hospital:

- Wheezing, severe shortness of breath, skin rashes.
- Yellowing of the whites of the eyes or skin.
- Severe pain in the stomach or chest area.

Tell your doctor if you develop any of the following side-effects particularly if they become troublesome:

- Shortness of breath.
- Discomfort or enlargement of the breasts. In rare cases milk secretion from the breasts can occur.
- Feelings of tiredness, weakness or listlessness. These side-effects will usually go away after you have been taking the medicine for a few weeks.
- Changes in sex drive and a reduction of sperm count and volume of ejaculate.
- Changes in body weight.
- Dryness of the skin and scalp.
- Increased growth of hair on the head but reduced hair growth on the body.
- Lightening of hair colour.
- Female type of pubic hair growth.
- Less greasy skin and hair.

In rare case Cyproterone Acetate has caused symptoms of osteoporosis (fragile weak bones which are easily broken).

If you experience any unusual effects not listed above, tell your doctor or pharmacist.

Storing your medicine

Do not take this medicine after the expiry date shown on the carton. If you notice that the tablets are broken or have an unusual colour, take them back to your pharmacist for advice before taking them. Keep the medicine in a safe place where children cannot see or reach it.

Do not store above 25°C.

Store the tablets in the original packaging in order to protect them from moisture. Also keep the blisters in the outer carton in order to protect the tablets from light.

Remember this medicine is for you. Only a doctor can prescribe it for you. Never give it to others because it may harm them even if their symptoms are the same as yours.

This leaflet only applies to Cyproterone Acetate 50 mg Tablets.

This leaflet was prepared in March 2006.



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CYPROTERONE ACETATE 100MG TABLETS

PL 08137/0128

PRODUCT INFORMATION LEAFLET


PATIENT INFORMATION LEAFLET
CYPROTERONE ACETATE 100 mg TABLETS

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

What is in your medicine?

Each tablet contains 100 mg of the active ingredient Cyproterone Acetate.

Other ingredients: Lactose monohydrate, maize starch, pre-gelatinised maize starch, povidone, magnesium stearate, colloidal anhydrous silica.

Cyproterone Acetate 100 mg Tablets are available in blister packs of 84 tablets. Your pharmacist will dispense the number of tablets prescribed by your doctor.

Cyproterone Acetate belongs to a group of medicines called anti-androgens. Cyproterone Acetate blocks the actions of male sex hormones (androgens) which are released naturally in your body. It also reduces the production of androgens.

The Marketing Authorisation Holder and manufacturer responsible for batch release is Neolab Ltd, 57 High Street, Odiham, Hants, RG29 1LF.

Uses

It has been shown that the growth of tumours of the prostate gland may be dependent on male hormones. Since Cyproterone Acetate blocks the action of androgens and reduces the amount of androgens produced by the body, it can be used to help relieve the symptoms of a tumour of the prostate gland.

Before taking your medicine

Do not take this medicine if:

- You have had any allergic reaction (wheezing, runny nose, skin rashes) to Cyproterone Acetate, other similar medicines (steroids), or any of the other ingredients in the tablets.
- You are under 18 years of age.

Tell your doctor **immediately** as the medicine may not be suitable for you.

If you have any of the following conditions your doctor may give you Cyproterone Acetate Tablets but will take extra care:

- You have been told by your doctor that you have an intolerance to some sugars (e.g. lactose).
- You have liver disease.
- You have a history of blood clots (heart attack, stroke, thrombosis or embolism).
- You suffer from diabetes.
- You suffer from a condition called sickle-cell anaemia (abnormalities of the red blood cells).
- You suffer from, or have suffered from depression.

Also tell your doctor before you start taking this medicine if:

- You drink alcohol, even if it is not regularly.
- You are planning a family.

You should **NOT** drink alcohol whilst taking Cyproterone Acetate Tablets.

If you are diabetic and your doctor decides that you can still take Cyproterone Acetate Tablets, your doctor may alter the dose of medicine (oral antidiabetic treatments or insulin) required to treat your diabetes.

It is likely that your doctor will arrange regular blood tests whilst you are taking Cyproterone Acetate Tablets.

This medicine may make you feel tired or weak. If you are affected, do not drive or work machinery.

Please read the back of this leaflet.

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Taking your medicine

Follow your doctor's directions about when and how to take your medicine and look at the dispensing label on the carton. Your pharmacist will help you if you are not sure.

Cyproterone Acetate Tablets should be swallowed whole with a glass of water after meals. Do not reduce the dose or stop the treatment unless your doctor tells you to.

For adults including the elderly, the normal doses to help relieve the symptoms of a prostatic tumour are as follows:

- To reduce the possible worsening ('flare up') of a prostatic tumour, which can happen during the first few weeks of starting other treatments for prostatic tumours (e.g. Buserelin Injection), the usual daily dosage is 300 mg (one tablet three times a day). Sometimes the daily dosage may be reduced by your doctor to 200 mg (one tablet twice a day).
- In long term treatment where other treatments or surgery are unsuitable, the usual daily dosage is 200 mg to 300 mg (one tablet two or three times a day).
- To treat hot flushes caused by other treatments for prostatic tumours or following surgical removal of the testicles, the usual daily dosage is 50 mg to 150 mg.

What to do in case of an overdose

If you take too much of your medicine contact your doctor immediately.

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As with other medicines you may experience side effects.

If any of the following happen, **STOP** taking the medicine and tell your doctor **IMMEDIATELY** or go to the casualty department at your nearest hospital:

- Wheezing, severe shortness of breath, skin rashes.
- Yellowing of the whites of the eyes or skin.
- Severe pain in the stomach or chest area.

Tell your doctor if you develop any of the following side-effects particularly if they become troublesome:

- Shortness of breath.
- Discomfort or enlargement of the breasts. In rare cases milk secretion from the breasts can occur.
- Feelings of tiredness, weakness or listlessness. These side-effects will usually go away after you have been taking the medicine for a few weeks.
- Reduction of sperm count and volume of ejaculate.
- Changes in body weight.
- Dryness of the skin and scalp.
- Increased growth of hair on the head but reduced hair growth on the body.
- Lightening of hair colour.
- Female type of pubic hair growth.
- Less greasy skin and hair.

In rare case Cyproterone Acetate has caused symptoms of osteoporosis (fragile weak bones which are easily broken).

If you experience any unusual effects not listed above, tell your doctor or pharmacist.

Storing your medicine

Do not take this medicine after the expiry date shown on the carton. If you notice that the tablets are broken or have an unusual colour, take them back to your pharmacist for advice before taking them. Keep the medicine in a safe place where children cannot see or reach it.

Do not store above 25°C.

Store the tablets in the original packaging in order to protect them from moisture. Also keep the blisters in the outer carton in order to protect the tablets from light.

Remember this medicine is for you. Only a doctor can prescribe it for you. Never give it to others because it may harm them even if their symptoms are the same as yours.

This leaflet only applies to Cyproterone Acetate 100 mg Tablets.

This leaflet was prepared in March 2006.

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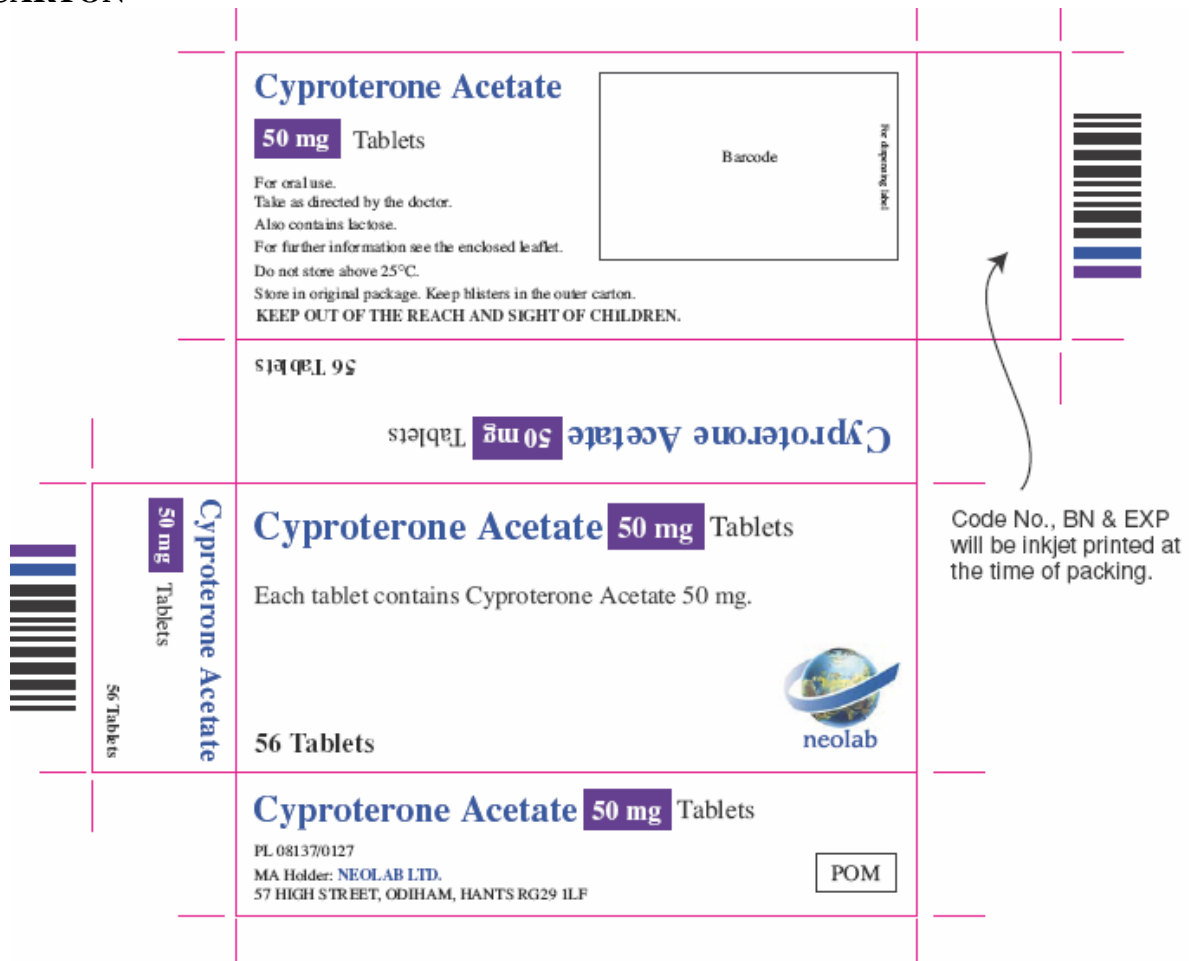
**CYPROTERONE ACETATE 50MG TABLETS
PL 08137/0127**

LABELLING

BLISTER FOIL



CARTON





**CYPROTERONE ACETATE 100MG TABLETS
PL 08137/0128**

LABELLING

BLISTER FOIL

COPVIA	Cyproterone Acetate 100 mg Tablets MA Holder Neolab Ltd	Cyproterone Acetate 100 mg Tablets MA Holder Neolab Ltd
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CARTON

84 Tablets	Cyproterone Acetate 100 mg Tablets	<p>Cyproterone Acetate 100 mg Tablets</p> <p>For oral use. Take as directed by the doctor. Also contains lactose. For further information see the enclosed leaflet. Do not store above 25°C. Store in original package. Keep blisters in the outer carton. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.</p> <p align="center">Barcode</p>	 <p>Code No., BN & EXP will be inkjet printed at the time of packing.</p>
		<p align="right">84 Tablets</p> <p align="right">Cyproterone Acetate 100 mg Tablets</p>	
		<p>Cyproterone Acetate 100 mg Tablets</p> <p>Each tablet contains Cyproterone Acetate 100 mg.</p> <p align="center">84 Tablets</p> 	
		<p>Cyproterone Acetate 100 mg Tablets</p> <p>PL 08137/0128 MA Holder: NEOLAB LTD. 57 HIGH STREET, ODIHAM, HANTS RG29 1LF</p> <p align="center">POM</p>	