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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted STD Chemicals Limited Marketing Authorisations (licences) for the medicinal products Cyproterone Acetate 50 mg and 100 mg Tablets (PL 36390/0011-2) on 26 May 2011. These medicines are only available on prescription from your doctor and are used to help relieve the symptoms of a tumour of the prostate gland. Cyproterone Acetate 50 mg and 100 mg Tablets can also be taken by males to control an over active sex drive.

The active ingredient, cyproterone acetate, belongs to a group of medicines called anti-androgens. These work by blocking the actions of male sex hormones (androgens) which are released naturally in your body. They also reduce the production of androgens.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of using Cyproterone Acetate 50 mg and 100 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
# CYPROTERONE ACETATE 50 MG AND 100 MG TABLETS
PL 36390/0011-2

## SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Cyproterone Acetate 50 mg and 100 mg Tablets (PL 36390/0011-2) to STD Chemicals Limited on 26 May 2011. The products are prescription-only medicines (POM) used for the management of patients with prostatic cancer (1) to suppress "flare" with initial leutinising hormone-releasing hormone (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. Cyproterone Acetate 50 mg and 100 mg Tablets are also used in the control of libido in severe hypersexuality and/or sexual deviation in the adult male.

The applications were submitted as abridged applications according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Cyproterone Acetate 50 mg and 100 mg Tablets (PL 08137/0127-8), which were granted Marketing Authorisations to Neolab Limited on 11 April 2006.

Cyproterone acetate, the active ingredient, is a progestational steroid with strong anti-androgen activities, which exerts a negative feedback on the hypothalamic receptors; thereby suppressing gonadotrophin release and hence secretion of testosterone (and other androgens) is reduced.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.
1. INTRODUCTION
These are abridged applications for Cyproterone Acetate 50 mg and 100 mg Tablets, submitted under Article 10c of Directive 2001/83/EC, as amended. The proposed Marketing Authorisation Holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The applications cross-refer to Cyproterone Acetate 50 mg and 100 mg Tablets (PL 08137/0127-8), which were granted Marketing Authorisations to Neolab Limited on 11 April 2006. The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed names of the products are Cyproterone Acetate 50 mg and 100 mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each tablet contains 50 mg or 100 mg of the active ingredient, cyproterone acetate. The tablets are packaged in polyvinylchloride/polvinylidene/aluminium blisters. These are packed into cardboard cartons with patient information leaflets in pack sizes of 56 (50 mg strength) and 84 (100 mg strength) tablets.

The proposed shelf-life (2 years) and storage conditions (“Do not store above 25°C. Store in original package. Keep blister in the outer carton.”) are consistent with the details registered for the cross-reference products.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing Authorisation Holder/Contact Persons/Company
STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW.

The Qualified Person (QP) responsible for pharmacovigilance is stated and his CV is included.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in line with the details registered for the respective cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

2.11 Bioequivalence
No bioequivalence data are required to support these simple abridged applications, as the proposed products are manufactured to the same formula and utilising the same processes as the reference products Cyproterone Acetate 50 mg and 100 mg Tablets (PL 08137/0127-8).

3. EXPERT REPORT
The applicant cross-refers to the data for Cyproterone Acetate 50 mg and 100 mg Tablets (PL 08137/0127-8), to which it claims identicality. This is acceptable.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the respective cross-reference products.

5. SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs)
The proposed Summaries of Product Characteristics are consistent with the details registered for the respective cross-reference products.
6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING

PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Carton and blister
The proposed artwork is consistent with the artwork registered for the respective cross-reference products and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSION
The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c, no new non-clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As the applications are for identical versions of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

As these are abridged applications submitted under Article 10c, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has not submitted a Risk Management Plan (RMP). As the applications are for identical versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active ingredient is well-established.

The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to previously granted applications for Cyproterone Acetate 50 mg and 100 mg Tablets (PL 08137/0127-8). No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the cross-reference products.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with cyproterone acetate is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
CYPROTERONE ACETATE 50 MG AND 100 MG TABLETS
PL 36390/0011-2

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation applications on 28 January 2011.
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 15 February 2011.
3. Following assessment of the application the MHRA requested further information relating to the dossiers on 07 April 2011.
4. The applicant responded to the MHRA’s request, providing further information on 18 May 2011.
5. The applications were determined on 26 May 2011.
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.

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 in the 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 started with one Cyproterone Acetate 50 mg Tablet twice daily. When a satisfactory result has been achieved, one should try to maintain the therapeutic effect with the lowest possible dose. When establishing the maintenance dose or when discontinuing the preparation, it is recommended to reduce the dose gradually. The daily dose should be divided and taken after the morning and evening meals.

The management of patients with prostatic cancer

The maximum daily dose is 300 mg.

Adults and the elderly:
To suppress "flare" with initial LHRH Analogue therapy:
Initially 2 tablets of Cyproterone Acetate 50 mg Tablets twice daily (200 mg) alone for 5-7 days, followed by 2 tablets of Cyproterone Acetate 50 mg Tablets twice daily (200 mg) for 3-4 weeks together with the LHRH analogue therapy in the dosage recommended by the marketing authorization holder (see SmPC of LHRH analogue).

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.

Additional information on special population (applies to all indications)
Children and adolescents:
Cyproterone acetate is not recommended for use in male children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Cyproterone acetate must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and still unstabilised axes of endocrine function cannot be ruled out.

Elderly patients:
There are no data suggesting the need for a dosage adjustment in elderly patients.

Patients with hepatic impairment:
The use of cyproterone acetate is contraindicated in patients with liver diseases (see section 4.4 and 4.8).

Patients with renal impairment:
The use of cyproterone acetate in patients with renal impairment has not been investigated. There are no data suggesting the need for dosage adjustment in patients with renal impairment (see section 5.2).

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

Cyproterone acetate must not be used in patients with meningioma or a history of meningioma.

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
Liver: 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, regularly during 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: The occurrence of thromboembolic events has been reported in patients using cyproterone acetate, although a causal relationship has not been established. Patients with a history of arterial or venous thrombotic/thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction), with a history of cerebrovascular
accidents or with advanced malignancies are at increased risk of further thromboembolic events, and 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 causal 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.

Medico-legal consideration: Doctors are advised to ensure that the fully informed consent of the patient to cyproterone acetate treatment is obtained, witnessed and can be verified

Lactose: 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.

Meningiomas: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above. If a patient treated with cyproterone acetate and is diagnosed with meningioma, treatment with cyproterone acetate must be stopped (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Diabetes: The requirement for oral antidiabetic treatment or insulin can change. See also section 4.4. At high therapeutic cyproterone acetate doses of three times 100 mg per day, cyproterone acetate may inhibit CYP2C8 (see below). Thiazolidinediones (i.e. the anti-diabetics pioglitazone and rosiglitazone) are substrates of CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

Cyproterone acetate can influence carbohydrate metabolism. Parameters of carbohydrate metabolism should be examined carefully in all diabetics before and regularly during treatment.
Chronic alcoholism: Alcohol appears to reduce the effect of cyproterone acetate, which is of no value in chronic alcoholics.

Other interactions: Clinical interaction studies have not been performed. However, since cyproterone acetate is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 inhibit the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as rifampicine, phenytoin and products containing St.John’s Wort may reduce the levels of cyproterone acetate.

Based on in vitro inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high cyproterone acetate doses of 100 mg three times per day. (This is three times the maximum total daily dose).

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMG-CoA inhibitors (statins) which are primarily metabolised by CYP3A4 are co-administered with high cyproterone acetate doses, since they share the same metabolic pathway.

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. Patients should be warned about this and if affected should not drive or operate machinery.

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

4.8 Undesirable effects
The most frequently observed adverse drug reactions (ADRs) in patients receiving cyproterone acetate are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving cyproterone acetate are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage and thromboembolic events.

The following approximate incidents were estimated from published reports of a number of small clinical trials and spontaneous ADR reports:
- very common: incidence $\geq 1:10$
- common: incidence $<1:10$ but $\geq 1:100$
- uncommon: incidence $<1:100$ but $\geq 1:1000$
- rare: incidence $<1:1000$ but $\geq 1:10,000$
- very rare: incidence $<1:10,000$
- not known (cannot be estimated from available data)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Very rare: Benign and malignant liver tumours which may lead to life threatening intra-abdominal haemorrhage (See section 4.4).
Not known: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25mg/day and above

Blood and lymphatic system disorders
Not known: Anaemia during long-term treatment

Immune system disorders
Rare: Hypersensitivity reactions

Endocrine disorders
Not known: Suppression of adrenocortical function.
**Metabolism and nutritional disorders**
Common: Changes in bodyweight during long-term treatment (chiefly weight gains in association with fluid retention).

**Psychiatric disorders**
Common: Depressive moods and restlessness (temporary).

**Vascular disorders**
Not known: Thromboembolic events, although a causal relationship has not been established (see section 4.4).

**Respiratory, thoracic & mediastinal disorders**
Common: Dyspnoea (see section 4.4).

**Hepatobiliary disorders**
Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, have been reported in patients treated with 200-300 mg cyproterone acetate (see section 4.4).

**Skin & subcutaneous tissue disorders**
Rare: Rash
Not known: Reduction of sebum production leading to dryness of the skin and consequently improvement of existing acne vulgaris has been reported as well as; 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.

**Musculoskeletal, connective tissue and bone disorders**
Not known: Osteoporosis (due to long-term androgen deprivation).

**Reproductive system disorders**
Very common: Decreased libido, erectile dysfunction, reduced sexual drive and inhibition of gonadal function. These changes are reversible after discontinuation of therapy.

Inhibition of spermatogenesis:
Very common: Sperm count and the volume of ejaculate is reduced. Infertility is usual, and there may be azospermia 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.

Gynaecomastia:
Common: Gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation.
Rare: Gaelectorrhoea and tender benign nodules.

Symptoms mostly subside after discontinuation of treatment or reduction of dosage.

**General and administration site disorders**
Common: Hot flushes, sweating, fatigue and lassitude

### 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-hydroxy-cyproterone. 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 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Ltd,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/05/2011

10 DATE OF REVISION OF THE TEXT
26/05/2011
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:*
The maximum daily dose is 300 mg

To suppress "flare" with initial LHRH Analogue therapy: Initially one Cyproterone Acetate 100 mg Tablet twice daily (200 mg) alone for 5-7 days, followed by one Cyproterone Acetate 100 mg Tablet twice daily (200 mg) for 3-4 weeks together with the LHRH analogue therapy in the dosage recommended by the marketing authorization holder (see SmPC of LHRH analogue).

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 50-150 mg/day. For this indication the dosage should be divided into 1-3 doses per day and taken after meals.

Additional information on special population (applies to all indications)

*Children and adolescents:* Cyproterone Acetate 100 mg Tablets are not recommended for use in male children and adolescents below 18 years of age due to lack of data on safety and efficacy.

Cyproterone Acetate 100 mg Tablets must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and still unstabilised axes of endocrine function cannot be ruled out.

*Elderly patients:*
There are no data suggesting the need for a dosage adjustment in elderly patients.
Patients with hepatic impairment:
The use of Cyproterone Acetate 100 mg Tablets are contraindicated in patients with liver diseases (see section 4.4 and 4.8).

Patients with renal impairment:
The use of Cyproterone Acetate 100 mg Tablets in patients with renal impairment has not been investigated. There are no data suggesting the need for dosage adjustment in patients with renal impairment (see section 5.2).

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

Cyproterone acetate must not be used in patients with meningioma or a history of meningioma.

4.4 Special warnings and precautions for use
Liver: 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, regularly during 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: The occurrence of thromboembolic events has been reported in patients using cyproterone acetate, although a casual relationship has not been established. Patients with a history of arterial or venous thrombotic/thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, myocardial infarction), with a history of cerebrovascular accidents or with advanced malignancies are at increased risk of further thromboembolic events, and 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 causal 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.

Lactose: 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.

Meningiomas: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above. If a patient treated with cyproterone acetate and is diagnosed with meningioma, treatment with cyproterone acetate must be stopped (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Diabetes: The requirement for oral antidiabetic treatment or insulin can change. See also section 4.4. At high therapeutic cyproterone acetate doses of three times 100 mg per day, cyproterone acetate may inhibit CYP2C8 (see below). Thiazolidinediones (i.e. the anti-diabetics pioglitazone and rosiglitazone) are substrates of CYP2C8 (increased blood levels of these anti-diabetics may require dose adjustment).

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

Chronic alcoholism: Alcohol appears to reduce the effect of cyproterone acetate.

Other interactions: Clinical interaction studies have not been performed. However, since cyproterone acetate is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 inhibits the metabolism of cyproterone acetate. On the other hand, inducers of CYP3A4 such as rifampicine, phenytoin and products containing St.John’s Wort may reduce the levels of cyproterone acetate.

Based on in vitro inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high cyproterone acetate doses of 100 mg three times per day. (This is three times the maximum total daily dose).

The risk of statin-associated myopathy or rhabdomyolysis may be increased when those HMG-CoA inhibitors (statins) which are primarily metabolised by CYP3A4 are co-administered with high cyproterone acetate doses, since they share the same metabolic pathway.

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 - patients should be warned about this and if affected should not drive or operate machinery.

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

The most frequently observed adverse drug reactions (ADRs) in patients receiving cyproterone acetate are decreased libido, erectile dysfunction and reversible inhibition of spermatogenesis.

The most serious ADRs in patients receiving Cyproterone Acetate are hepatic toxicity, benign and malignant liver tumours which may lead to intra-abdominal haemorrhage and thromboembolic events.

The following approximate incidents were estimated from published reports of a number of small clinical trials and spontaneous ADR reports:
- very common: incidence ≥ 1:10
- common: incidence <1:10 but ≥1:100
- uncommon: incidence <1:100 but ≥1:1000
- rare: incidence<1:1000 but ≥ 1:10,000
- very rare: incidence < 1:10,000
- not known (cannot be estimated from available data)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very rare: Benign and malignant liver tumours which may lead to life threatening intra-abdominal haemorrhage (See section 4.4).
Not known: The occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25mg/day and above.

Blood and lymphatic system disorders

Not known: Anaemia during long-term treatment

Immune system disorders

Rare: Hypersensitivity reactions

Endocrine disorders

Not known: Suppression of adrenocortical function.

Metabolism and nutritional disorders

Common: Changes in bodyweight during long-term treatment (chiefly weight gains in association with fluid retention).

Psychiatric disorders

Common: Depressive moods and restlessness (temporary).

Vascular disorders

Not known: Thromboembolic events, although a causal relationship has not been established (see section 4.4).

Respiratory, thoracic & mediastinal disorders

Common: Dyspnoea (see section 4.4).

Hepatobiliary disorders

Common: Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, have been reported in patients treated with 200-300 mg cyproterone acetate (see section 4.4).

Skin & subcutaneous tissue disorders

Uncommon: Rash
Not known: Reduction of sebum production leading to dryness of the skin and improvement of existing acne vulgaris has been reported as well as; 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.

Musculoskeletal, connective tissue and bone disorders
Not known: Osteoporosis (due to long-term androgen deprivation).

Reproductive system disorders
Very common: Decreased libido, erectile dysfunction, reduced sexual drive and inhibition of gonadal function. These changes are reversible after discontinuation of therapy.

Inhibition of spermatogenesis:
Very common: 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.

Gynaecomastia:
Common: Gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation.
Rare: Galectorrhoea and tender benign nodules.
Symptoms mostly subside after discontinuation of treatment or reduction of dosage.

General and administration site disorders
Common: Hot flushes, sweating, fatigue and lassitude.

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-hydroxyacyproterone. 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 Special precautions for disposal
No specific recommendations applicable

7 MARKETING AUTHORISATION HOLDER
STD Chemicals Ltd,
Hillbrow House,
Hillbrow Road,
Esher,
Surrey,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/05/2011

10 DATE OF REVISION OF THE TEXT
26/05/2011
PATIENT INFORMATION LEAFLET

CYPROTERONE ACETATE 50 mg & 100 mg TABLETS
(cypoterone acetate)

The name of this medicine is Cypoterone Acetate 50 mg and 100 mg Tablets which will be referred to as Cypoterone Tablets throughout this leaflet.

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others; it may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Cypoterone Tablets are and what they are used for
2. Before you take Cypoterone Tablets
3. How to take Cypoterone Tablets
4. Possible side effects
5. How to store Cypoterone Tablets
6. Further information

1. WHAT CYPORERONE TABLETS ARE AND WHAT THEY ARE USED FOR

The active ingredient in your tablets is cypoterone acetate, which belongs to a group of medicines called anti-androgens. These work by blocking the actions of male sex hormones (androgens) which are released naturally in your body. They also reduce the production of androgens.

It has been shown that the growth of tumors of the prostate gland may be dependent on male hormones. Since cypoterone 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.

It can also be taken by men to control an overactive sex drive.

2. BEFORE YOU TAKE CYPORERONE TABLETS

Do not take Cypoterone Tablets if you:
- are allergic (hypersensitive) to cypoterone acetate, or any of the other ingredients in Cypoterone Tablets (these are listed in section 6. Further information)
- are under 16 years of age
- have been diagnosed with a meningioma (a generally benign tumor of the brain or the skull). You should ask your physician if you are in doubt.
- have kidney failure
- have liver disease

If you are being treated for an overactive sex drive you should not take this medicine if you:
- suffer from liver disease
- have or have previously had lumps, other than in your prostate gland
- suffer from any illness making you thin, weak or tired
- have a history of blood clots (heart attack, stroke, thrombosis or embolism)
- suffer from diabetes
- suffer from a condition called sickle cell anaemia (abnormalities of the red blood cells)
- have had or have ever suffered from depression

Take special care with Cypoterone Tablets

Before you take Cypoterone Tablets you should tell your doctor if you:
- have liver disease
- have a history of blood clots (heart attack, stroke, thrombosis or embolism)
- suffer from diabetes
- suffer from a condition called sickle cell anaemia (abnormalities of the red blood cells)
- have or have ever suffered from depression
- drink alcohol even if it is not regularly
- are planning a family
- you are diabetic and your doctor has advised you to take Cypoterone Tablets (unless your diabetes is not being controlled, your doctor will prescribe Cypoterone Tablets)
- the risk of serious side effects is increased if you are diabetic
- you are pregnant
- you are breast-feeding
- you have had or are getting skin cancer
- you have or have had liver disease
- you have or have had a history of blood clots (heart attack, stroke, thrombosis or embolism)
- you have or have had diabetes
- you have or have ever suffered from depression
- you are planning a family
- you are taking any other medicines including those obtained without a prescription

Certain medicines can interfere with the effectiveness of each other. It is particularly important to tell your doctor or pharmacist before taking this medicine if you are also on:
- thiazolidinediones, pioglitazone and rosiglitazone used in the treatment of diabetes
- levothyroxine, thyroid hormone, used to treat hypothyroidism
- fluoxetine (used to treat depression)
- fluoxetine, fluvoxamine, paroxetine and sertraline (used to treat depression)
- tetracyclines, used to treat bacterial infection
- rifampicin, used to treat tuberculosis
- fluoxetine, used to treat depression

Rifampicin used to treat Mycobacterium tuberculosis and HIV infections
- St John's Wort (Hypericum perforatum), a herbal remedy
- anticoagulants or other medicines that affect the blood clotting

Take your medicine with food and drink.

Cypoterone Tablets should be taken after meals. You should avoid drinking alcohol whilst taking these tablets.

Pregnancy and breast-feeding

This medicine is not to be used in women.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive or operate tools or machines because this medicine may make you feel tired or weak, particularly within the first few weeks of taking it.

Important information about some of the ingredients of Cypoterone Tablets

This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, consult your doctor before taking this medicine.

3. HOW TO TAKE CYPORERONE TABLETS

Always take Cypoterone Tablets exactly as your doctor has told you to do so. You should check with your doctor or pharmacist if you are not sure.

Dosage

For adults and the elderly, the dose for Cypoterone Tablets is dependent on the condition for which your doctor has prescribed them.
For the control of an overactive sex drive the usual dose is 50 mg twice a day. Your doctor can only prescribe this medicine once he has explained what the tablets will do and you have agreed to take them.

To help relieve the symptoms of a prostate cancer the usual dose is as follows: to reduce the possible worsening of a prostate cancer, which can happen during the first few weeks of starting other treatments for prostate cancer, the usual daily dose is two 50 mg tablets twice daily (100 mg) alone for 5-7 days, followed by two 50 mg tablets twice daily (200 mg) for 14 days together with another medicine.

- in long-term treatment where other treatments or surgery are unsuitable, the usual daily dose is 200 mg to 300 mg (one 100 mg tablet or two 50 mg tablets twice or three times a day).
- to treat hot flushes caused by other treatments for prostate cancer or following surgical removal of the testicles, the usual daily dose is 50 mg to 150 mg (one 50 mg tablet once or three times a day).

Cypionate Tablets are not recommended for use in male children and adolescents below 18 years of age.

Method of administration
Cypionate Tablets should be taken by mouth after meals.

If you take more Cypionate Tablets than you should
If you have accidentally taken more than the prescribed dose, contact your nearest hospital casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining tablets with you.

If you forget to take Cypionate Tablets
If you miss a dose do not worry. Take another as soon as you remember and then go on as before. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cypionate Tablets can cause side effects, although not everybody gets them. If you get any of the following symptoms after taking these tablets you should contact your doctor or pharmacist immediately:

- any sudden weakness, difficulty in breathing or dizziness, skin rash
- yellowing of the whites of the eyes or skin
- severe pain in the stomach or chest area
- severe liver failure which can be associated with fluid retention
- blood in the urine
- liver problems, some with severe or even fatal have been reported with high-dose cypionate acetate treatment (200-300 mg daily)
- diarrhoea or enlargement of the breasts
- hot flushes, sweating, tenderness

Rare side effects (probably affecting fewer than 1 in 1000 people):

- allergic reactions
- tender lumps in the breasts and in rare cases secretion of milk from the nipples may occur. These symptoms usually disappear when treatment is stopped
- very rare (probably affecting fewer than 1 in 10,000 people)
- some forms of liver cancer (malignant liver tumours) which may lead to bleeding in the abdomen
- an increase in the occurrence of meningiomas has been reported in association with longer term use (years) of cypionate acetate at doses of 250 mg/day and above
- changes in blood caused by a type of anaemia (feeling of weakness, tiredness). These side effects usually go away after you have been taking your tablets for a few weeks
- dryness of the skin, scaly and hair
- increased growth of hair on the head but reduced hair growth on the body
- tightening of hair colour
- female type of pubic hair growth

If any of these side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CYPIONATE TABLETS

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date (Exp.) stated. The expiry date refers to the last day of that month.

Do not store your tablets above 25°C. Store your tablets in the original package. Keep blister packs in the outer carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cypionate Tablets contain:

Cypionate Tablets contain 50 mg or 100 mg of the active ingredient cypionate acetate.

The other ingredients are lactose monohydrate, maize starch, pregelatinised maize starch, povidone, magnesium stearate and colloidal anhydrous silica.

What Cypionate Tablets look like and the contents of the pack:

Cypionate Acetate 50 mg Tablets are white, circular tablets with a central break line on one side and plain on the other. Cypionate Acetate 50 mg Tablets are available in a pack size of 56 tablets.

Cypionate Acetate 100 mg Tablets are white circular tablets with a break line on one side and CPA 100 marked on the other. Cypionate Acetate 100 mg Tablets are available in a pack size of 64 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
The Product Licence holder is STD Chemicals Ltd, Hillrow House, Hillrow Road, Esher, Surrey, KT10 9HW. The manufacturer responsible for batch release is Nicolai Ltd, 57 High Street, Ockham, Has, RG25 1LF.

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