SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

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PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ANDROCUR DEPOT Solution for injection

ANDROCUR 300 mg Depot contains cyproterone acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 ml ampoule contains cyproterone acetate 300 mg in oily solution.

Excipients with known effects:
Benzyl benzoate 618,60 mg/ml

For full excipients see section 6.1

3. PHARMACEUTICAL FORM

Clear, colourless to faintly yellowish oily solution in 3 ml amber glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of drive in sexual deviations in males; Antiandrogen treatment in inoperable carcinoma of the prostate.

4.2 Posology and method of administration

Posology

The injections must be administered very slowly. ANDROCUR Depot is strictly for intramuscular injection. Special care must be given to avoid intravasal injection.

Reduction of drive in sexual deviations in males

In general, 1 ampoule of ANDROCUR Depot is given as a deep intramuscular injection every 10 to 21 days. If, in exceptional cases, the effect is inadequate, 2 ampoules can be given every 10 to 21 days, preferably as 1 ampoule each in the right and left gluteal muscles. Efficacy can be maintained by injection intervals ranging from 10 to 21 days.

The duration of cyproterone acetate treatment should be defined on an individual basis. When the therapeutic result is considered to be satisfactory, an attempt should be made to reduce the dosage by gradually increasing the intervals between injections.

To stabilise the therapeutic effect it is necessary to administer ANDROCUR Depot over a protracted period of time, if possible with the simultaneous use of psychotherapeutic measures.

Antiandrogen treatment in inoperable carcinoma of the prostate

After orchidectomy:
300 mg (1 ampoule) every 2 weeks as a deep IM injection.
Without orchidectomy:
300 mg (1 ampoule) weekly as a deep IM injection.
Treatment should not be interrupted, nor the dosage reduced after improvement or remissions have occurred.

Special populations

Paediatric population

ANDROCUR is not recommended for use in male children and adolescents below 18 years of age due to a lack of data on safety and efficacy.
ANDROCUR Depot must not be given before the conclusion of puberty since an unfavourable influence on longitudinal growth and the still unstabilised axes of endocrine function cannot be ruled out.

Geriatric patients

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

Patients with hepatic impairment

The use of ANDROCUR Depot is contraindicated in patients with liver diseases (i.e. as long as liver function values have not returned to normal).

Patients with renal impairment

There are no data suggesting the need for a dosage adjustment in patients with renal impairment.

4.3 Contraindications

- Liver diseases.
- Dubin-Johnson syndrome, Rotor syndrome.
- Previous or existing liver tumours (only if these are not due to metastases from carcinoma of the prostate).
- Presence or history of meningioma
- Wasting diseases (with the exception of inoperable carcinoma of the prostate).

- Depression.
- Previous or existing thromboembolic processes.
- Severe diabetes with vascular changes.
- Sickle-cell anaemia.
- Hypersensitivity to any of the components of ANDROCUR Depot.

4.4 Special warnings and precautions for use

Liver

Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, has been observed in patients treated with ANDROCUR. At dosages of 100 mg and above also cases with fatal outcome have been reported. Most reported fatal cases were in males with advanced carcinoma of the prostate. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, ANDROCUR should be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case ANDROCUR should be continued only if the perceived benefit outweighs the risk.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate. If a patient treated with ANDROCUR is diagnosed with meningioma, treatment with cyproterone containing product, including ANDROCUR must be permanently stopped (see section '4.3'***).***

In very rare cases benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage, have been observed after the use of ANDROCUR. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, a liver tumour should be included in the differential-diagnostic considerations.

Thromboembolic events

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

In patients with inoperable carcinoma of the prostate, presenting with a history of thromboembolic processes or suffering from sickle-cell anaemia or from severe diabetes with vascular changes, a careful risk: benefit evaluation must be carried out in each individual case before ANDROCUR is prescribed. Prolactin levels may increase with higher doses of ANDROCUR.

Anaemia

Anaemia has been reported during treatment with ANDROCUR. Therefore, the red-blood cell count should be checked regularly during treatment.

Shortness of breath

A sensation of shortness of breath may occur under high-dosed treatment with ANDROCUR. The differential diagnosis in such cases must include the stimulating effect on breathing known for progesterone and synthetic progestogens which is accompanied by hypocapnia and compensated respiratory alkalosis and which is not considered to require treatment.

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

ANDROCUR should be used with caution in cardiovascular disease, ischaemic heart disease, cerebrovascular disease and hypertension.

During treatment, liver function, adrenocortical function and the red blood-cell count should be checked regularly.

Diabetes mellitus

Strict medical supervision is necessary if the patient suffers from diabetes.

Adrenocortical function

During treatment, adrenocortical function should be checked regularly, as preclinical data suggest a possible suppression due to the corticoid-like effect of ANDROCUR with high doses (see section '5.3').

Other conditions

As with all oily solutions, ANDROCUR Depot must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can in some cases lead to signs and symptoms such as cough, dyspnoea and chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhydrosis, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, e.g. by administration of oxygen.

In the indication "reduction of drive in sexual deviations", the drive-reducing effect of ANDROCUR Depot can be diminished under the disinhibitory influence of alcohol.

4.5 Interaction with other medicines and other forms of interaction

Although clinical interaction studies have not been performed it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir and other strong inhibitors of CYP3A4 will inhibit the metabolism of ANDROCUR as it is metabolised by CYP3A4. On the other hand, inducers of CYP3A4 such as e.g. rifampicin, phenytoin and products containing St John's Wort may reduce the levels of ANDROCUR.

Based on *in vitro* inhibition studies, an inhibition of the cytochrome P450 enzymes CYP2C8, 2C9, 2C19, 3A4 and 2D6 is possible at high therapeutic ANDROCUR doses of 3 times 100 mg per day.

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

4.6 Fertility, pregnancy and lactation

Treatment with ANDROCUR depot (for use in men) is not indicated for women.

4.7 Effects on ability to drive and use machines

It should be pointed out to patients whose occupation demands great concentration (e.g. road users, machine operators) that ANDROCUR Depot can lead to tiredness and diminished vitality and can impair the ability to concentrate.

4.8 Undesirable effects

The most frequently observed adverse drug reactions (ADRs) in patients receiving ANDROCUR are decreased libido (≥ 1/10) , erectile dysfunction (≥ 1/10) and reversible inhibition of spermatogenesis (≥ 1/10).

The most serious adverse drug reactions (ADRs) in patients receiving ANDROCUR are hepatic toxicity (≥ 1/100 and < 1/10) , benign and malignant liver tumours (< 1/10 000) which may lead to intra-abdominal haemorrhage (frequency unknown), and thromboembolic events (≥ 1/10 000 and < 1/1000) .

The frequencies of ADRs reported with ANDROCUR are summarized in the table below. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 and < 1/100), rare (≥ 1/10,000 and < 1/1,000) and very rare (< 1/10,000). The ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated are listed under “not known”.

System Organ Class MedDRA	Very common	Common	Uncommon	Rare	Very rare	Not Known
Neoplasms benign, malignant and unspecified					Benign and malignant liver tumours	Meningiomas
Blood and lymphatic system disorders				Thromboembolic events	Changes in the number of red blood cells	Anaemia
Immune system disorders				Hypersensitivity reaction		
Endocrine disorders					Reduction of adrenocortical function Increase in prolactin levels	
Metabolism and nutrition disorders		Weight increased or weight decreased				
Psychiatric disorders	Libido decreased Erectile dysfunction	Depressed mood Restlessness (temporary)				
Vascular Disorders						Pulmonary oil microembolism, Vasovagal reactions, Thromboembolic events
Respiratory, thoracic and mediastinal disorders		Shortness of breath				

Gastrointestinal disorders						Intra-abdominal haemorrhage
Hepato-biliary disorders		Hepatic toxicity, including jaundice, hepatitis, hepatic failure				
Skin and subcutaneous tissue disorders			Rash			
Musculoskeletal and connective tissue disorders						Osteoporosis
Reproductive system and breast disorders	Reversible inhibition of spermatogenesis	Gynaecomastia Feeling of tension in the breasts				
General disorders and administration site conditions		Fatigue Hot flushes Sweating				

Under treatment with ANDROCUR Depot, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible after discontinuation of therapy.

Over the course of several weeks, ANDROCUR Depot inhibits spermatogenesis as a result of the antiandrogenic and antigonadotropic actions. Spermatogenesis recovers gradually within a few months of discontinuing the therapy.

ANDROCUR Depot may lead to gynaecomastia (sometimes combined with tenderness to touch of the mamillae) which usually regresses after withdrawal of the preparation. Permanent enlargement of the mammary glands may occur. Galactorrhoea and benign nodules have been reported.

Long-term androgen deprivation with ANDROCUR may lead to osteoporosis.

Meningiomas have been reported in association with long-term use (several years) of ANDROCUR doses of 25 mg and above. (see section “4.3” and section “4.4”)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “ **6.04 Adverse Drug Reaction Reporting Form”,** found online under SAHPRA’s publications: http://www.sahpra.org.za/Publications/index/8

4.9 Overdose

See “Section 4.8”. Treatment is supportive and symptomatic.

5. PHARMACEUTICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: http: Antiandrogens, Plains
ATC Code: G03HA01

Cyproterone acetate has antiandrogenic, progestational and antigonadotropic effects.

The stimulating effect of male sex hormones on androgen dependent structures and functions is weakened or abolished by cyproterone acetate.

The inherent progestational activity exerts a negative feedback on the hypothalamic receptors so leading to a reduction in gonadotropin release, and hence to diminished production of androgens.

Cyproterone acetate has a central inhibiting effect. The antigonadotropic effect leads to a reduction of testosterone synthesis in the testes and, hence, to a reduction of the serum concentration of testosterone.

Cyproterone acetate inhibits competitively the effect of androgens at androgen-dependent target organs.

In males, under treatment with cyproterone acetate, sexual drive and potency are reduced and gonadal function is inhibited. These changes are reversible following discontinuation of the therapy.

The antigonadotropic effect of cyproterone acetate is also exerted when the substance is combined with GnRH agonists. The initial increase of testosterone provoked by this substance group is decreased by cyproterone acetate.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of cyproterone acetate after IM injection can be assumed to be complete.

Distribution

Cyproterone acetate is about 96 % plasma protein bound, almost exclusively to plasma albumin. Because protein binding is non-specific, changes in sex hormone binding globulin (SHBG) levels do not affect the pharmacokinetics of cyproterone acetate.

After intramuscular administration, cyproterone acetate was released slowly and completely from the intramuscular depot. Maximum drug levels in the serum of 180 ± 54 ng/ml were achieved after about 2 to 3 days. Thereafter, drug serum levels declined with a terminal half-life of 4 ± 1,1 days. The total clearance of cyproterone acetate from serum was determined to be 2,8 ± 1,4 ml/min/kg.

Biotransformation

Cyproterone acetate is metabolised by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15β-hydroxy derivative. Phase I metabolism of cyproterone acetate is mainly catalysed by the cytochrome P450 enzyme CYP3A4.

Elimination

Cyproterone acetate is partly excreted unchanged with bile fluid. Most of the dose is excreted in form of metabolites with urine and faeces.

Linearity/non-linearity

According to the long half-life of the terminal disposition phase from plasma (serum) and the dosing interval of 7 days, an accumulation of cyproterone acetate can be expected in the serum during repeated administration. An equilibrium between the release of the drug from the depot and the elimination can be expected after about 5 weeks.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity

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 systemic exposures that might be expected to occur in the recommended dose regimens for cyproterone acetate. *In vivo* consequences of cyproterone acetate treatment were the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats, and an increase of mutation frequency in transgenic rats carrying a bacterial gene as target for mutations.

Clinical experience and well conducted epidemiological trials to date would not support an increased incidence of hepatic tumours in man. Nor did investigations into the tumorigenicity of cyproterone acetate in rodents reveal any indication of a specific tumorigenic potential.

However, it must be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl Benzoate excipient
Nitrogen excipient
Castor oil refined excipient

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Protect from light. Store below 30 °C.

6.5 Nature and contents of container

Amber glass ampoules of 3 ml.

6.6 Special precautions for disposal

Not Applicable

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8 REGISTRATION NUMBER

R/21.12/184

9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

12 February 1991

10 DATE OF REVISION OF THE TEXT

14/12/2021