SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

APPLICANT: BAYER (PTY) LTD
PRODUCT NAME: ANDROCUR 10 mg
DOSAGE FORM: Tablet
STRENGTHS: 10,0 mg

PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF MEDICINE

ANDROCUR 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

Each ANDROCUR 10 mg tablet contains cyproterone acetate 10 mg.

Contains 59,9 mg lactose per tablet (see section 4.4).

For full list of excipients see “section 6.1”

3 PHARMACEUTICAL FORM

White to faintly yellowish tablets, scored on one side, with an embossed "BW" in a regular hexagon on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moderately severe signs of androgenisation in women of child-bearing age, e.g.:

- moderately severe forms of hirsutism.
- moderately severe androgen-dependent loss of scalp hair (moderately severe androgenetic alopecia).
- severe and moderately severe forms of acne and seborrhoea.

4.2 Posology and method of administration

Posology

Pregnant women must not take ANDROCUR, pregnancy must be excluded.

For the duration of ANDROCUR therapy women of child-bearing age must also receive a combination oral contraceptive. This will provide the necessary contraceptive protection and will stabilise the menstrual cycle. Dosage and directions for use as per the package insert of that product should be strictly adhered to.

Prior to commencing ANDROCUR treatment it is always necessary for the patient to receive one complete cycle of a combination oral contraceptive.

Extra non-hormonal methods (with the exception of the rhythm and temperature methods) should be employed during the first 3 weeks of the first cycle, which may be shorter than 4 weeks. Subsequent cycles should then be regular.

In the subsequent cycle of the combination oral contraceptive (second cycle) which starts the very next day after completion of the first pack of combination oral contraceptive, ANDROCUR treatment is commenced on the 5th day of the menstrual cycle (1st day of bleeding = 1st day of the menstrual cycle) regardless of whether bleeding has stopped or not, i.e. 5th to 19th day of cycle inclusive.

The first ANDROCUR 10 mg tablet is taken from the memo-pack out of one of the blisters marked with the corresponding day of the week (for example "Mon" for Monday) and swallowed whole with some liquid. It does not matter at what time of the day the patient takes the tablet, but once she has selected a particular time - preferably after her breakfast or evening meal - she should keep to it.

From now on the patient must take a tablet every day in the direction indicated by the arrows on the pack (altogether 14 tablets) and as the last tablet of the ANDROCUR treatment, the one from the section marked with number "15".

Every 28 days (the usual duration of a menstrual cycle), the above dosage regimen is to be followed.

Women receiving the cyclical combined ANDROCUR and combination oral contraceptive therapy, should keep to a particular time of the day for tablet taking. If more than 12 hours elapse from this time contraceptive protection in this cycle may be reduced. The use of these two products should nevertheless be continued according to instructions, ignoring the missed tablet or tablets, in order to avoid premature bleeding in this cycle. However, an additional non-hormonal method of contraception (with the exception of the rhythm and temperature methods) is to be employed for the rest of the cycle.

The length of treatment is determined by the severity of the pathological signs of androgenisation and their response to treatment. Treatment may have to last several months. Acne and seborrhoea usually respond sooner than hirsutism or alopecia.

Missed bleeding

If, in exceptional cases, no bleeding occurs during the tablet-free interval, the treatment must be interrupted, and pregnancy must be excluded before tablet-taking is resumed.

Missed tablets

If the patient forgets to take combined oral contraceptive tablet at the usual time, she must take it within the next 12 hours at the latest. If more than 12 hours elapse from the time that she normally takes her combined oral contraceptive tablet, contraceptive protection may be reduced in this cycle. Attention is drawn to the special notes (especially on contraceptive reliability and to the missed pill recommendations) in the product information for combined oral contraceptive. If bleeding fails to occur after this cycle, pregnancy must be excluded before tablet-taking is resumed. Missed ANDROCUR tablets may diminish the therapeutic

efficacy and may lead to intermenstrual bleeding. The missed ANDROCUR tablet should be disregarded (no double dose should be taken to make up for the missed tablet) and tablet taking resumed at the regular time together with combined oral contraceptive tablet.

Method of administration

Oral Use

Special populations

Paediatric population

ANDROCUR is only indicated for use in female patients after conclusion of puberty. There are no data suggesting the need of a dosage adjustment.

Geriatric patients

ANDROCUR 10 mg is indicated only in women of childbearing age.

Patients with hepatic impairment

The use of ANDROCUR is contraindicated in women 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

- Pregnancy
- Lactation
- Liver diseases
- A history of jaundice or persistent itching during a previous pregnancy
- A history of herpes of pregnancy
- Dubin-Johnson syndrome
- Rotor syndrome
- Previous or existing liver tumours
- Wasting diseases
- Depression
- Previous or existing thromboembolic processes
- Diabetes with vascular changes
- Sickle-cell anaemia.

4.4 Special warnings and precautions for use

Before starting treatment, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out and pregnancy must be excluded.

Liver

During treatment, liver functions should be checked regularly. Liver function tests should be performed pre-treatment, at regular intervals during treatment and whenever any symptoms or signs suggestive of hepatotoxicity occurs. If hepatotoxicity is confirmed, ANDROCUR should be withdrawn.

Cases of 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.

Diabetes

In diabetics, carbohydrate metabolism should also be monitored particularly carefully.

Strict medical supervision is necessary if the patient suffers from diabetes because the requirement for oral antidiabetics or insulin can change during ANDROCUR treatment (see section 4.3).

Combined treatment

If, during the combined treatment, slight spotting occurs, tablet-taking should not be interrupted. However, if persistent or recurrent bleeding occurs at irregular intervals, a gynaecological examination must be carried out to exclude organic disease. With regard to the necessary additional use of combined contraceptive tablet, attention is also drawn to all the data relevant to this preparation.

Lactose

ANDROCUR 10 mg contains 59,9 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should not take this medicine.

4.5 Interaction with other medicines and other forms of interactions

Although clinical interaction studies have not been performed, since this drug is metabolized 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 e.g. rifampicin, phenytoin and products containing St. John´s wort may reduce the levels of cyproterone acetate.

4.6 Fertility, pregnancy, and lactation

ANDROCUR is contraindicated during pregnancy and lactation

In a study with 6 women who received a single oral dose of 50 mg CPA, 0.2 % of the dose was excreted in breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed.

4.8 Undesirable effects

Summary of the safety profile

Benign & malignant liver tumors (frequency not known)

The most commonly reported adverse drug reactions (ADRs) in patients receiving ANDROCUR 10 mg is spotting, weight increase and depressed mood.

The most serious ADRs in patients receiving ANDROCUR 10 mg are benign and malignant liver tumors which may lead to intra-abdominal hemorrhage.

Tabulated list of adverse reaction

The ADRs reported with ANDROCUR 10 mg are reported in the table below based on post marketing data and cumulative experience with ANDROCUR for which a frequency could not be estimated.

System Organ Class MedDRA	**Frequency not known**
Neoplasms benign and malignant	Benign & malignant liver tumors*
Immune system disorders	Hypersensitivity reaction
Metabolism and nutrition disorders	Weight increased; Weight decreased
Hepato-biliary disorders	Hepatic function abnormal, Jaundice, Hepatitis
Psychiatric disorders	Depressed mood, Libido decreased, Libido increased
Gastrointestinal disorders	Intra-abdominal hemorrhage
Skin and subcutaneous tissue disorders	Rash
Reproductive system and breast disorders	Breast tenderness, Ovulation inhibited, Spotting*

***** For further information see section 4.4

Description of selected adverse reactions

Ovulation is inhibited under the combined treatment, so that a state of infertility exists.

With regard to the necessary additional use of combined contraceptive, attention is drawn to the special notes on undesirable effects contained in the product information of combined contraceptive.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any

suspected reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications :https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Acute toxicity studies following single administration showed that cyproterone acetate, the active ingredient of ANDROCUR, can be classified as practically non-toxic. Nor is any risk of acute intoxication to be expected after a single inadvertent intake of a multiple of the dose required for therapy. (See section 4.8.)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antiandrogens, plain
ATC Code: G03HA01

ANDROCUR is an antiandrogenic hormone preparation

Androgen-dependent conditions such as pathological hair growth in hirsutism, androgenetic alopecia and increased sebaceous gland function in acne and seborrhea, are favorably influenced by competitive displacement of the androgens at the target organs. The reduction of the androgen concentration which results from the antigonadotropic property of cyproterone acetate has an additional therapeutic effect.

These changes are reversible following discontinuation of the therapy.

During the combined treatment with combined contraceptive, ovarian function is inhibited.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, cyproterone acetate is completely absorbed over a wide dose range. The absolute bioavailability of cyproterone acetate is almost complete (88% of dose).

Distribution

The ingestion of 10 mg of cyproterone acetate will give maximum serum levels of about 75 ng/ml at about 1.5 hours. Thereafter, drug serum levels decrease in two disposition phases characterized by half-lives of 0.8 hours and 2.3 days.

The total clearance of cyproterone acetate from serum was determined to be 3.6 ml/min/kg. Cyproterone acetate is 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.

Biotransformation

Cyproterone acetate is metabolized by various pathways, including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-hydroxy derivative.

Elimination

Some dose parts are excreted unchanged with bile fluid. Most of the dose is excreted in the form of metabolites at a urinary-to-biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days.
Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).

Linearity/non-linearity

According to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, an accumulation of cyproterone acetate by a factor of 2 - 2.5 can be expected in the serum during one treatment cycle.

5.3 Preclinical safety data

Systemic toxicity

Preclinical data reveal no specific risk for humans based on conventional studies of repeated dose toxicity.

Embryotoxicity/teratogenicity

Investigations into embryotoxicity showed no effects indicative of a teratogenic effect following treatment during organogenesis before development of the external genital organs. Administration of cyproterone acetate during the hormone-sensitive differentiation phase of the genital organs led to signs of feminization in male fetuses following higher doses. Observation of male newborn children who had been exposed in utero to cyproterone acetate did not show any signs of feminization. However, pregnancy is a contraindication for the use of ANDROCUR.

Genotoxicity and carcinogenicity

Recognized 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, the DNA-adduct level in dog liver cells were extremely low.

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 was 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 do not support an increased incidence of hepatic tumors 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 tumors.

On the whole, the available data do not raise any objection to the use of ANDROCUR in humans if used in accordance with the directions for the given indication and at the recommended dose.

6 PHARMACEUTICAL PATICULARS

6.1 List of excipients

lactose monohydrate
maize starch
povidone 25
colloidal anhydrous silica
magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Memo-packs of 15 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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/21.12/159

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 April 1989

10 DATE OF REVISION OF TEXT

14 December 2021