## 1. NAME OF THE MEDICINAL PRODUCT

Androcur 10

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Cyproterone acetate

One tablet contains 10 mg cyproterone acetate (CPA).

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablet

White to pale yellow tablets with a breaking score line on one side and embossed with ‘BW’ in a regular hexagon on the other. The score line is to break the tablet for ease of swallowing; not to divide the tablet into equal doses.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of pronounced signs of virilisation in women, which make hormone therapy necessary:

- severe forms of acne, when it is accompanied by inflammation and the formation of nodes (Acne papulopustulosa, Acne nodulocystica) or if there is a risk of scarring,
- moderate to severe forms of hirsutism,
- moderate to severe forms of androgenic alopecia.

Cyproterone acetate 10 mg is indicated for pronounced signs of virilisation in women, which make hormone therapy necessary if satisfactory results could not be obtained with medicinal products containing low-dose cyproterone or with other treatment options. When treating acne, hormone treatment should be weighed against systemic antibiotic treatment

### 4.2 Posology and method of administration

*Method of administration*

Oral administration

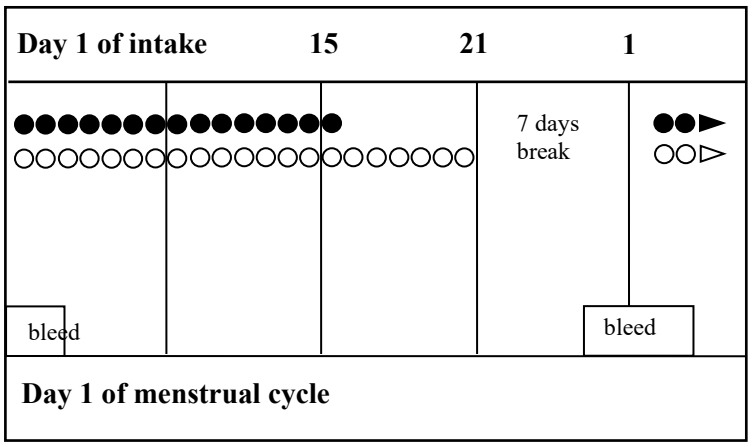
*Dosage*

Pregnant women may not take Androcur. Consequently, pregnancy has to be excluded prior to the start of therapy (see section 4.4). Androcur 10 mg has to be used in combination with a suitable oestrogen or a suitable progestogen-oestrogen combination (combined oral contraceptive 'pill'), in order to ensure necessary contraceptive protection and to avoid irregular bleeding.

This combination therapy shall be carried out as follows:

Both products have to be started on day 1 of the cycle (day 1 of menstruation).

One Androcur 10 mg tablet has to be taken daily from day 1 to day 15 of the combination therapy. Additionally, from day 1 to day 21, a suitable oestrogen or a suitable progestogen-oestrogen combination has to be taken (combined oral contraceptive 'pill').




● 1 Androcur 10 mg tablet

○ 1 coated tablet of the oestrogen or of the progestogen-oestrogen combination used (oral contraceptive 'pill')

Both products have to be started on day 1 of the cycle (day 1 of menstruation). Only women, who are amenorrhoeic, begin immediately with the therapy prescribed by the doctor; in this case, day 1 of intake is considered as day 1 of menstruation and further calculated according to the recommendations.

The first Androcur 10 mg tablet is removed from the field of the calendar pack, which corresponds to the day of the week on which the course is started. Then, one further tablet will be taken each day in direction of the arrow and end with the tablet from the field marked '15'. For a further 6 days, only the oestrogen or the progestogen-oestrogen combination (combined oral contraceptive 'pill'), whichever is being used, will be taken.

During the subsequent seven-day break, withdrawal bleeding will occur. Four weeks after having started taking the tablets, i.e. on the same day of the week, the next combined

treatment will be started, irrespective of whether the bleeding has already stopped or is still ongoing.

Since women may not become pregnant while receiving Androcur 10 mg, they must properly adhere to the treatment regimen.

*Missed medication*

If a dose of Androcur-10 mg has been missed at its usual time, the combination treatment should be continued according to schedule without taking the missed tablet (a double dose should not be taken to make up for the forgotten dose of Androcur 10 mg). The missed dose of Androcur 10 mg can result in reduced efficacy and intermenstrual bleeding.

If the oestrogen or the progestogen-oestrogen combination (combined oral contraceptive 'pill'), whichever is being used, has been missed at its usual time, they must be taken, at the latest within 12 hours following the usual time. The contraceptive effect becomes questionable if more than 36 hours have elapsed since the previous administration. Nevertheless, the combination therapy should be continued according to schedule without the missed coated tablet, in order to avoid premature withdrawal bleeding. The advice and recommendations contained in the package leaflet and in the summary of product characteristics (in particular with regard to the contraceptive effect in the event of missing doses) of the oestrogen or the progestogen-oestrogen combination, whichever is being used, have to be followed.

*Absence of the withdrawal bleed*

If there is no bleed at the end of that particular cycle, pregnancy must be ruled out before tablet taking is resumed.

*Length of use*

The length of treatment depends upon the type, severity and the individual response to treatment of the virilisation signs. Acne generally responds more quickly to therapy than does hirsutism or alopecia.

If no or only insufficient success has been obtained, in the case of
- severe acne with at least 6 months of therapy or
- alopecia and hirsutism with at least 12 months of therapy

an increase in the cyproterone-acetate dose may be considered in combination with oestrogen or a suitable oestrogen-progestogen combination.

When therapy has been adequately successful, treatment may be continued with a low-dose cyproterone acetate-oestrogen combination or an anti-androgen sex steroid.

***Additional information on special populations***

*Children and adolescents*

Androcur 10 mg may be used in female patients only after completion of puberty. Before the end of puberty, an adverse effect of Androcur 10 mg on the growth in length cannot be completely ruled out. There are no data, which require a dosage adjustment.

The safety and efficacy of Androcur in children and adolescents under 18 years has not been established in clinical trials.

*Geriatric Patients*

Androcur 10 mg is only indicated in women of childbearing potential.

*Patients with liver disease*

The use of Androcur 10 mg is contraindicated in patients with liver disease for as long as the liver values have not returned to normal.

*Patients with renal impairment*

The pharmacokinetics of cyproterone acetate in patients with renal impairment has not been investigated.

## 4.3 Contraindications

Do not use Androcur 10 mg

- in the event of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in the event of liver diseases (including elimination disorders, such as Dubin-Johnson syndrome and Rotor syndrome),
- in the event of previous or existing liver tumours,
- in patients with wasting diseases (because of transient catabolic action)
- in the event of known or suspected malignant diseases,
- in patients with meningiomas or meningiomas in their history,
- in the event of severe chronic depression,
- in the event of previous or existing thromboembolic events,
- in the event of severe Diabetes mellitus with vascular changes,
- in the event of sickle-cell anaemia,
- during pregnancy,
- whilst breast-feeding,

- in the event of undiagnosed vaginal bleeding,
- in the event of idiopathic jaundice pregnancy or severe pruritus during pregnancy or respectively Pemphigoid gestationis in the medical history,
- Androcur 10 should not be given to patients before the conclusion of puberty or to those whose maturation is incomplete.

Moreover, the information has to be followed concerning contraindications and reasons for immediate discontinuation, contained in the respective package leaflets and summary of product characteristics of the oestrogen or progestogen-oestrogen combination (combined oral contraceptive 'pill'), whichever is being used.

## 4.4 Special warnings and precautions for use

*General*

Before starting therapy, a thorough general (along with examining the urine for sugar) gynaecological examination (including an examination of the breasts and a cytological cervical smear) must be conducted for the differential diagnosis of androgenisation signs and to detect risk conditions. Pregnancy has to be ruled out due to the risk of feminising male foetuses.

Treatment has to be in combination with a suitable oestrogen or a suitable progestogen-oestrogen combination (oral contraceptive 'pill'), which supports the therapeutic effect of Androcur 10 mg in order to ensure necessary contraceptive protection and a good cycle control. Although cyproterone acetate also has a contraceptive effect in combination with an oestrogen or a suitable cyproterone acetate-oestrogen combination contraceptive, it should not be used exclusively for contraception but only used in women who have to be treated for their androgen-dependent skin disorders (see section 4.1). Women who are being treated with CPA in combination with an oestrogen and/or with a suitable oestrogen-progestogen combination, should not take any additional oral contraceptive during this treatment. Regular intake has to be observed in order to achieve contraceptive protection. All of the instructions have to be observed, which pertain to the oestrogen or progestin-oestrogen combination used.

*Absence of the withdrawal bleed*

The absence of a withdrawal bleed during the seven-day break may be an indication of pregnancy. Therefore, in such a case, combination treatment may only be resumed when pregnancy has been ruled out with certainty.

*Liver*

The liver function should be monitored regularly during treatment. Liver function should be checked prior to the start of treatment, at regular intervals during treatment, as well as whenever symptoms or signs suggest hepatotoxicity. If the suspicion of hepatotoxicity has been confirmed, Androcur should be discontinued. Benign and malignant liver tumours, which may lead to life-threatening intra-abdominal haemorrhage, have been observed as a result of using Androcur. A liver tumour should be considered in the differential diagnosis when severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in connection with the use of cyproterone acetate mainly at doses of 25 mg per day and over. The risk of meningioma increases with increasing cumulative doses of cyproterone acetate (see section 5.1). High cumulative doses can be attained by long-term use (several years) or in cases of shorter duration with high daily doses.
Patients should be monitored for meningioma in accordance with clinical practice. If a patient treated with Androcur 10 mg tablets is diagnosed with meningioma, treatment with Androcur 10 mg tablets and other medicinal products containing cyproterone acetate must be discontinued permanently (see section ”Contraindications”).

There is some evidence to indicate that the risk for meningioma may reduce following cessation of treatment with cyproterone acetate.

*Carbohydrate metabolism*

Increased blood-sugar levels have been observed in diabetics treated with Androcur. Carbohydrate metabolism should, therefore, be monitored carefully in women with Diabetes mellitus before and regularly during treatment with Androcur since the required dose of oral antidiabetic drugs or insulin can change. (see section 4.3.).

*Combination therapy: Procedure in the event of intermenstrual bleeding*

Treatment should not be interrupted in the event of bleeding during the week cycle. Spotting often subsides by itself. In the event of heavy or recurrent minor bleeding, a gynaecological examination is required to exclude organic disease.

*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).

Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Androcur 10 mg.

## 4.5 Interaction with other medicinal products 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 inhibit the metabolism of cyproterone acetate, since this medicinal product is metabolised by CYP3A4. On the other hand, inducers of CYP3A4 such as rifampicin, phenytoin, and products containing St. John's wort may reduce the level of cyproterone acetate.

## 4.6 Pregnancy and lactation.

Androcur is contraindicated during pregnancy or whilst breast-feeding (see section 4.3).

Administration of CPA during the hormone-sensitive differentiation phase of the genital organs caused signs of feminisation in male foetuses following high doses in animal studies. Animal studies on embryo-toxicity revealed no evidence of teratogenicity.

Based on 100,000 woman-years of CPA exposure, there were 0.2 cases reported, in which male foetuses were exposed *in utero* to CPA. In the majority of these cases, the women involved had taken 2 mg CPA per day during the first trimester of pregnancy. In isolated cases, 100 mg CPA were taken per day up to the second trimester or respectively 2 mg

CPA per day up to the third trimester of pregnancy. None of the male neonates in these cases showed any signs of feminisation.

Nonetheless, pregnancy is a contraindication for the use of Androcur.

CPA passes into breast milk. About 0.2% of the maternal dose can be transferred to the nursing infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

The most commonly reported adverse drug reactions, (ADRs) in patients taking Androcur 10 mg are intermenstrual bleeding, weight gain and depression.

The most serious adverse drug reactions involved benign and malignant liver tumours, which may cause intra-abdominal haemorrhage.

The following table lists the adverse drug reactions, which have been reported in connection with Androcur 10 mg. They are based on post-marketing data and experience gained with Androcur, for which frequency cannot be estimated.

The best suited MedDRA terminology was used to describe any certain reaction, and its synonyms and associated diseases.

| **System Organ Class**<br>**MedDRA** | **Rare** | **Frequency not known**<br>(cannot be estimated from the available data) |
|---|---|---|
| Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps) | Meningioma | Benign and malignant liver tumours* |
| Immune system disorders | | Hypersensitivity reactions |
| Metabolism and nutrition disorders | | Weight gain<br>Weight loss<br>Rise in blood sugar in diabetics |

| | | |
|---|---|---|
| Hepatobiliary disorders | | Abnormal hepatic function<br>Jaundice*<br>Hepatitis* |
| Psychiatric disorders | | Depression<br>Decrease in libido<br>Increase in libido |
| Gastrointestinal disorders | | Intra-abdominal haemorrhage |
| Skin and subcutaneous tissue disorders | | Skin reactions |
| Reproductive system and breast disorders | | Pain, breast tenderness or breast enlargement, in particular at the start of treatment<br>Irregular or absent menstrual bleeding<br>Spotting* |

* For more information see section 4.4.

The occurrence of meningiomas (single and multiple) has been reported in connection with the use of cyproterone acetate (see section 4.4).

Stomach complaints and nausea have been commonly reported in connection with medicinal products, which contain cyproterone acetate as their active ingredient.

Furthermore, due to the concomitant administration of a suitable oestrogen or a suitable progestogen-oestrogen combination (oral contraceptive, 'pill'), the information, contained in the section, Undesirable effects, of the pertinent summary of product characteristics and package leaflet, has to be additionally observed.

Although cyproterone acetate also has a contraceptive effect in combination with an oestrogen or a suitable cyproterone acetate-oestrogen combination contraceptive, it should not be used exclusively for contraception but only used in women who have to be treated for their androgen-dependent skin disorders (see section 4.1). Women who are being treated with CPA in combination with an oestrogen and/or with a suitable oestrogen-progestogen combination, should not take any additional oral contraceptive during this treatment. Regular intake has to be observed in order to achieve contraceptive protection.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

### 4.9 Overdose

Studies on acute toxicity after single doses revealed, that cyproterone acetate, the active component of Androcur 10 mg, has to be classified as virtually non-toxic. Similarly unlikely is an acute intoxication following a single accidental ingestion of multiple therapeutic doses.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-androgen, pure

ATC Code: G03 HA

The anti-androgen properties of CPA, the active ingredient of Androcur 10 mg, permits specific therapy of androgenisation in women. Pathological, androgen-dependent conditions such as hirsutism, androgenetic alopecia and increased sebaceous-gland function, seen in acne and seborrhoea, are favourably influenced by competitive inhibition of androgens at the target organs. Remission occurs independently of whether increased androgen values or increased peripheral sensitivity cause the disorder. The reduction of the androgen concentration, which results from the antigonadotropic property of cyproterone acetate, has an additional therapeutic effect.

CPA, which is also a potent progestogen, would result in reduced cycle control should it be administered continuously as a single drug. This can be diminished or avoided by combining it with an oestrogen or a suited progestogen-oestrogen product (oral contraceptive).

*Meningioma*

Based on a French epidemiological cohort study, a cumulative dose-dependent relationship was observed between cyproterone acetate and meningiomas. This study was based on data from the French health insurance (CNAM) and included a population of 253,777 women, who were taking tablets of 50-100 mg cyproterone acetate. The incidence of meningioma treated by surgery or radiation therapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥ 3 g) and women with only low exposure to cyproterone acetate (cumulative dose < 3 g). A correlation was revealed between the cumulative dose and occurrence.

| Cumulative dose of cyproterone acetate | Incidence rate (in patient years) | $HR_{adj}$ (95% CI)[a] |
|---|---|---|
| Mild exposure (< 3 g) | 4.5/100,000 | Ref. |
| Exposure up to ≥ 3 g | 23.8/100,000 | 6.6 [4.0-11.1] |
| 12 to 36 g | 26/100,000 | 6.4 [3.6-11.5] |
| 36 to 60 g | 54.4/100,000 | 11.3 [5.8-22.2] |
| more than 60 g | 129.1/100,000 | 21.7 [10.8-43.5] |

*Adjusted according to age as a time-dependent variable and oestrogen at start of application

A cumulative dose of, for example, 12 g may correspond to one year of treatment with 50 mg/day for 20 days per month.

## 5.2 Pharmacokinetic properties

*Absorption*

CPA is completely absorbed in a wide dose range. The absolute bioavailability of CPA is 88 % of dose.

*Distribution*

Peak concentrations of approximately 75 ng/mL may be expected about 1.5 hours after oral ingestion of 10 mg CPA. Subsequently, the drug serum levels decrease biphasically, characterised by half-lives of about 0.8 hours and 2.3 days. The total clearance of CPA from serum is 3.6 mL/min/kg.

CPA is present in serum almost exclusively in protein-bound form. About 3.5 – 4 % of total CPA levels are present unbound, and the remainder is bound to albumin. Since CPA binding to sex hormone binding globulin (SHBG) is not detectable, changes in sex hormone binding globulin (SHBG) levels do not affect the pharmacokinetics of CPA.

*Metabolisation*

CPA is metabolised by various pathways including hydroxylation and conjugation. The main metabolite in serum is 15β-hydroxy-CPA.

*Elimination*

Some CPA dose parts are excreted unchanged with the bile fluid. Most of the dose, however, is excreted in form of metabolites via urine and faeces at a ratio of 3:7 with a half-life of 1.9 days. Metabolites are eliminated from plasma at a similar rate (half-life of 1.7 days).

*Steady-state conditions*

That the active substance accumulates in serum by about the factor of 2 to 2.5 with daily administration within one treatment cycle is to be expected by virtue of the long terminal half-life of CPA.

Smoking does not affect the pharmacokinetics of CPA.

## 5.3 Preclinical safety data

*Systemic toxicity*

Preclinical data reveal no particular hazard for humans based on the conventional studies on chronic toxicity.

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 (300mg/day).

*Reproduction toxicity, teratogenicity*

Animal experimental studies on embryo-foetal development toxicity and on the development of the genitalia did not indicate any teratogenic potential that exceeded the known effects on differentiation of the male genital tract.

*Genotoxicity, carcinogenicity*

Recognised first-line tests of genotoxicity gave no indication of a mutagenic effect when conducted with CPA. However, further tests showed that CPA was capable of producing adducts with DNA (and an increase in DNA repair activity) in liver cells from rats, monkeys and humans. The DNA-adduct concentration was extremely low in rabbit liver cells.

This DNA-adduct formation occurred at systemic exposures that might be expected to occur in the recommended dose regimens. One consequence of *in-vivo* treatment was the increased incidence of focal, possibly pre-neoplastic, liver lesions in which cellular enzymes were altered in female rats and an increased mutation frequency in transgenic rats, carrying a bacterial gene as a mutation marker.

The clinical significance of these findings is currently uncertain. Clinical experience to date do not indicate an increased incidence of hepatic tumours in man.

Investigations into the tumourigenicity of CPA in rodents did not reveal any results that differed fundamentally from those obtained with other steroid hormones. It must be borne in mind, however, that sex steroids can promote the growth of certain hormone-dependent tissue and tumours.

Available results verify that there are no concerns about taking Androcur 10 mg as prescribed in the proper range of use and at the recommended dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate

Maize starch

Polyvidone 25

Magnesium stearate

Silica Colloidal anhydrous

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to store at room temperature.

### 6.5 Nature and contents of container

Blister packs made of polyvinyl chloride and hardened aluminium

Pack size:

15 tablets

### 6.6 Special precautions for disposal

No special requirements.

## 7. MANUFACTURER

Bayer Weimar GmbH und Co. KG, Weimar, Germany.

## 8. REGISTRATION HOLDER

Beyer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.

Revised in May 2022 according to MOHs guidelines