AUSTRALIAN PRODUCT INFORMATION

BRENDA-35 ED®

(cyproterone acetate/ethinylestradiol) tablet

1 NAME OF THE MEDICINE

Cyproterone acetate and Ethinylestradiol

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BRENDA-35 ED contains the synthetic progestogen, cyproterone acetate and the synthetic estrogen, ethinylestradiol.

Each beige active tablet contains ethinylestradiol 35 micrograms and cyproterone acetate 2 mg.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Tablet, sugar coated

BRENDA-35 ED ACTIVE TABLET: Beige, round tablets

BRENDA-35 ED PLACEBO TABLET: White, round tablets

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BRENDA-35 ED is indicated for:

- The treatment of signs of androgenisation in women such as severe acne (involving inflammation or nodularity or risk of scarring) where prolonged oral antibiotics or local treatment alone has not been successful, or idiopathic hirsutism of mild to moderate degree.

- BRENDA-35 ED will also provide effective oral contraception in this patient group. It should not be used in combination with other hormonal contraceptives (see Section 4.3 CONTRAINDICATIONS).

If the hirsutism has only recently appeared or has lately intensified to a considerable extent, the cause (i.e. androgen-producing tumour or an adrenal enzyme defect) must be clarified by differential diagnosis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year.

BRENDA-35 ED is to be taken regularly in order to achieve therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of BRENDA-35 ED is similar to the usual regimen of most of the COCs. Thus, the same administration rules must be considered. The irregular intake of BRENDA-35 ED can lead to intermenstrual bleeding and could deteriorate the therapeutic and contraceptive reliability. Therapy should not be initiated unless pregnancy has been excluded.

Duration of Treatment

Treatment will probably need to be continued for about 6 months and probably much longer to gain an acceptable therapeutic effect, especially if BRENDA-35 ED is being used for the treatment of excessive hair. The length of use depends on the severity of the symptoms of androgenisation and their response to treatment. Acne and seborrhoea usually respond sooner than hirsutism. The need to continue treatment should be

evaluated periodically by the treating doctor. It is possible that the original condition will recur once treatment with BRENDA-35 ED is stopped.

BRENDA-35 ED should be withdrawn 3 to 4 cycles after the treated condition has completely resolved. Repeat course of BRENDA-35 ED may be given if the androgen-dependent condition(s) recur. In case of a restart with BRENDA-35 ED (following a 4 week or greater tablet-free interval), the increased risk of VTE should be considered (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

How to take BRENDA-35 ED

One tablet is to be taken daily. The tablets must be taken in the order directed on the pack at about the same time every day, with some liquid as needed. Tablet taking should be continuous for 28 consecutive days, starting with a tablet corresponding to that day of the week from the red section of the BRENDA-35 ED pack.

If a woman starts on a Monday, Tuesday, Wednesday, Thursday or Friday, her first tablet is a white placebo tablet, while if she starts on a Saturday or Sunday her first tablet will be a beige active tablet. Thereafter, one tablet is taken daily, following the arrows marked on the pack, until all tablets have been taken. Each subsequent pack is started the day after the last tablet of the previous pack.

Withdrawal bleeding should usually occur on day 2 to 3 after the last beige active tablet is taken and may not have finished before the next pack is started.

How to start BRENDA-35 ED

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Additional non-hormonal contraceptive methods must be used for the first 14 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive/COC), vaginal ring

The woman should start with BRENDA-35 ED on the day after the last active tablet of her previous COC.

In case where a vaginal ring has been used, the woman should start taking BRENDA-35 ED on the day of removal.

Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch from the minipill on any day, from an implant or the IUS on the day of its removal, or from an injectable when the next injection would be due, but in all of these cases she should be advised to additionally use a non-hormonal method of contraception for the first 14 days of tablet-taking.

Following first trimester abortion

The woman may start immediately. Additional non-hormonal contraceptive methods are necessary for the first 14 days of tablet-taking.

After childbirth or a second trimester abortion

Women should be advised to start 21 to 28 days after delivery or second-trimester abortion. Additional non-hormonal contraceptive methods are necessary for the first 14 days of tablet-taking. If intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

BRENDA-35 ED should not be used in breastfeeding women (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Lactation).

Additional Contraceptive Precautions

When additional contraceptive precautions are required, the woman should be advised to either to abstain from sex, or to use a barrier method of contraception, such as a cap (or diaphragm) plus spermicide, or for her partner to use a condom. Rhythm methods should not be advised as the pill disrupts the cyclical changes associated with the natural menstrual cycle e.g. changes in temperature and cervical mucus.

How to Manage Reduced Reliability

When BRENDA-35 ED is taken according to the directions for use, the occurrence of pregnancy is highly unlikely. However, the reliability of contraceptive protection may be reduced under the following circumstances:

- Management of Missed Tablets

Missed white pills from the last row of the blister are placebo (inactive, hormone-free) tablets and thus can be disregarded. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase. **The following advice only refers to missed beige active tablets (rows 1-3 of the blister)**:

If the woman is **less than 12 hours late** in taking any beige active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If the woman is **more than 12 hours late** in taking any beige active tablet, contraceptive protection may be reduced. The more tablets are missed and the closer they are to the regular placebo tablet interval, the higher the risk of a pregnancy.

The management of missed tablets can be guided by the following two basic rules:

1. 'Active tablet'-taking must never be discontinued for longer than 7 days.

2. Seven days of uninterrupted 'active tablet'-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- Week 1 of active tablets

The woman should take the last missed beige active tablet as soon as she remembers, even if this means taking two beige active tablets in one day at the same time, and then continue to take tablets at her usual time. Additional contraceptive precautions should be taken for the next 7 days.

If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

- Week 2 of active tablets

The woman should take the last missed beige active tablet as soon as she remembers, even if this means taking two beige active tablets at the same time. She then continues to take tablets at her usual time, provided that the woman has taken her tablets correctly in the 7 days preceding the first missed beige active tablet. There is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one beige active tablet, the woman should be advised to use extra precautions for 7 days.

- Week 3 of active tablets

The risk of reduced reliability is imminent because of the forthcoming white placebo tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed beige active tablet the woman has taken all tablets

correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The woman should take the last beige active missed tablet as soon as she remembers, even if this means taking two beige active tablets at the same time. She then continues to take tablets at her usual time until the beige active tablets are taken. The 7 white placebo tablets must be discarded. The next pack must be started right away. The woman is unlikely to have a withdrawal bleed until the end of the active tablets of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet interval, the possibility of a pregnancy should be considered.

- Advice in case of Gastrointestinal Disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after taking a beige active tablet, the advice concerning management of missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she should take the extra tablet(s) needed from another pack.

4.3 CONTRAINDICATIONS

Preparations containing estrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during their use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
    - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
    - Known hereditary or acquired predisposition for VTE, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilisation
    - A high risk of VTE due to the presence of multiple risk factors
- Presence or risk factor(s) for venous or arterial thrombosis [ATE] may also constitute a contraindication (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
    - Current ATE or history of ATE (e.g. myocardial infarction [MI] or stroke) or prodromal condition (e.g. transient ischaemic attack [TIA], angina pectoris)
    - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant)
    - History of migraine with focal neurological symptoms
    - A high risk of ATE due to multiple risk factors or to the presence of one serious risk factor such as:

  - Diabetes mellitus with vascular symptoms
  - Severe hypertension
  - Severe dyslipoproteinaemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease whereby liver function values have not returned to normal
- BRENDA-35 ED is contraindicated for concomitant use with the medicinal products glecaprevir, pibrentasvir, sofosbuvir, velpatasvir, voxilaprevir, ombitasvir, paritaprevir or dasabuvir and combinations of these (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Meningioma or history of meningioma
- Concomitant use with another hormonal contraceptive
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Lactation
- Hypersensitivity to any of the ingredients in BRENDA-35 ED.

BRENDA-35 ED is not for use in men.

BRENDA-35 ED is composed of the progestogen cyproterone acetate and the estrogen ethinylestradiol and is administered for 21 days of a monthly cycle. It has a similar composition to that of a COC. The clinical and epidemiological experience with estrogen/progestogen combinations like BRENDA-35 ED is predominantly based on combined oral contraceptives (COCs). Therefore, the following warnings related to the use of COCs apply also for BRENDA-35 ED.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below are present, the benefits of BRENDA-35 ED should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether BRENDA-35 ED should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of COCs containing ethinylestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction (MI), stroke, deep venous thrombosis (DVT) and pulmonary embolism (PE). These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use.

The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective 3-armed cohort study (EURAS and LASS) suggest that this increased risk is mainly present during the first 3 months.

A large, prospective 3-armed cohort study has shown that the incidence rate of VTE ranged from 8 to 10 per 10,000 woman years (WY) in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the incidence rate of VTE is approximately 4.4 per 10,000 woman years in non-pregnant non-COC users, and ranged from 20 to 30 per 10,000 WY in pregnancy or the post-partum period.

Overall the risk of VTE in users of low estrogen dose (< 50 µg ethinylestradiol) COCs are two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Epidemiological studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of BRENDA-35 ED than in users of levonorgestrel-containing COCs.

The user group of BRENDA-35 ED is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome.

An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinylestradiol cannot be excluded.

The increased risk of VTE during the postpartum period must be considered. See Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.6 FERTILITY, PREGNANCY AND LACTATION).

VTE may be life-threatening or may have a fatal outcome (in 1-2% of the cases).

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

BRENDA-35 ED is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50)

- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
- Other medical conditions associated with VTE include:
    - Cancer
    - Systemic lupus erythematosus
    - Haemolytic uraemic syndrome
    - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
    - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of BRENDA-35 ED (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if BRENDA-35 ED has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in VTE.

Symptoms of VTE (DVT and PE)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of DVT can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg
- pain or tenderness in the leg which may be felt only when standing or walking
- increased warmth in the affected leg; red or discoloured skin on the leg

Symptoms of PE can include:

- sudden onset of unexplained shortness of breath or rapid breathing
- sudden coughing which may be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- severe light headedness or dizziness
- rapid or irregular heartbeat

Some of these symptoms (e.g. "shortness of breath", "coughing") are nonspecific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for ATE (e.g. MI, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. BRENDA-35 ED is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for ATE

- increasing age, particularly above 35 years
- smoking
- hypertension
- obesity
- positive family history (ATE ever in a sibling or parent especially at relatively early age e.g. below 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
    - Diabetes mellitus
    - Polycystic ovary syndrome
    - Hyperhomocysteinaemia
    - Valvular heart disease
    - Atrial fibrillation
    - Dyslipoproteinaemia
    - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

The user group of BRENDA-35 ED is likely to include patients that may have an inherently increased cardiovascular risk.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of stroke can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia; sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause
- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of MI can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest arm, or below the breastbone
- discomfort radiating to the back, jaw, throat, arm, stomach
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

Tumours

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver

tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Malignancies may be life-threatening or have a fatal outcome.

Meningioma

The occurrence of meningiomas (single and multiple) has been reported in association with use of cyproterone acetate, especially at high doses of 25 mg and above and for prolonged time. If a patient is diagnosed with meningioma, any cyproterone containing treatment, including BRENDA-35 ED, must be stopped, as a precautionary measure.

Other Conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis and otosclerosis-related hearing loss.

In women with hereditary angiooedema exogenous estrogens may induce or exacerbate symptoms of angio-oedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or from previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in women with diabetes taking low-dose COCs (containing < 50 μg ethinylestradiol). However, women with diabetes should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

If in women suffering from hirsutism, symptoms have recently developed or increased substantially, the causes (androgen-producing tumour, adrenal enzyme defect) must be clarified by differential diagnosis.

Each beige active tablet contains 30.97 mg of lactose monohydrate and each white placebo tablet contains 48.25 mg of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose- galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of BRENDA-35 ED use, guided by the CONTRAINDICATIONS and PRECAUTIONS (see Sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and should be repeated periodically. In general, an annual examination is recommended. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family

history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections (STIs) including Human Immunodeficiency Virus (HIV) infections and AIDS

BRENDA-35 ED does not protect against STIs, including HIV infections (AIDS). The woman should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced Efficacy

The contraceptive efficacy of BRENDA-35 ED may be reduced in the event of missed beige active tablets (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Management of missed tablets), vomiting, or diarrhoea during beige active tablet taking (see Section 4.2 DOSE AND METHOD OF ADMINSTRATION - Advice in gastrointestinal disturbances) or concomitant medication (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Reduced Cycle Control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women, withdrawal bleeding may not occur during the placebo tablet interval. If the COC has been taken according to the directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION) prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

Alanine transaminase (ALT) elevations

In patients treated with hepatitis C antiviral medications including glecaprevir, pibrentasvir, ombitasvir, paritaprevir or dasabuvir, ALT elevations may occur in women using ethinylestradiol-containing medications such as CHCs. Prescribers should consult the relevant antiviral medicine product safety information. Patients taking a CHC should therefore be switched to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy.

Use in Hepatic Impairment

BRENDA-35 ED is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see Section 4.3 CONTRAINDICATIONS).

Use in Renal Impairment

BRENDA-35 ED has not been specifically studied in renally impaired patients.

Use in the Elderly

BRENDA-35 ED is not indicated after menopause.

Paediatric Use

BRENDA-35 ED is only indicated after menarche.

Effects on Laboratory Tests

The use of preparations like BRENDA-35 ED may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicines on BRENDA-35 ED

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women prescribed any of these medicines should temporarily use a barrier method in addition to BRENDA-35 ED or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the beige active tablets in the BRENDA-35 ED, the white placebo tablets should be omitted and the next pack be started.

Substances increasing the clearance of BRENDA-35 ED (diminished efficacy of BRENDA-35 ED by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John's Wort (*Hypericum perforatum*).

Substances with **variable effects on the clearance of BRENDA-35 ED:**

When co-administered with COCs, many HIV/hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) can increase or decrease plasma concentration of estrogen or progestogen. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestogen or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 35 µg ethinylestradiol.

Influence of BRENDA-35 ED on other Medication

Estrogen/progestogen preparations like BRENDA-35 ED may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). ALT elevations have also been observed with HCV anti-viral medicinal products including glecaprevir/ pibrentasvir. Patients taking a CHC should therefore be switched to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy.

Note: The product information of concomitant medications should be consulted to identify potential interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available

Use in Pregnancy

Pregnancy Category: Category B3

Animal studies showed that the drug combination of ethinylestradiol and cyproterone acetate or cyproterone acetate alone (given at high doses) can cause signs of feminisation in male fetuses if given during the phase of differentiation of the fetal male genital organs. The relevance of these findings to man is not known. Isolated cases of inadvertent use of BRENDA-35 ED during pregnancy have so far given no indications of a corresponding risk in humans. Despite this, the possibility must be considered that the use of BRENDA-35 ED during the hormone-sensitive phase of differentiation of the genital organs in male fetuses (from about the 45^{th} day of pregnancy) might cause signs of feminisation. For this reason, BRENDA-35 ED is contraindicated during pregnancy.

If pregnancy occurs during treatment with BRENDA-35 ED, further intake must be stopped.

Use in Lactation

The use of BRENDA-35 ED is contraindicated during lactation as small amounts of cyproterone acetate are excreted in breast milk. Estrogen containing oral contraceptives may decrease the quantity and quality of breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Various adverse reactions have been associated with oral contraceptive use. The most serious reactions associated with the use of oral contraceptives are discussed under **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

The most commonly reported adverse reactions with BRENDA-35 ED are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness.

They occur in ≥ 1 % of users.

Serious adverse reaction is thromboembolism.

In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether its use should be discontinued.

System Organ Class	Common (≥ 1/100 to <1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to ≤ 1/1000)
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhoea	
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	Depressed mood Altered mood	Decreased libido	Increased libido
Nervous system disorders	Headache	Migraine	
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme
Eye disorders			Contact lens intolerance
Reproductive system and breast disorders	Breast pain Breast tenderness	Breast hypertrophy	Vaginal discharge Breast discharge
Immune system disorders			Hypersensitivity
Investigations	Increased weight		Decreased weight
Vascular disorders			Thromboembolism

Other Adverse Effects

Eyes disorders: cataract.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no reports of serious deleterious effects from overdose. On the basis of general experience with COCs, symptoms that may occur in case of overdose of beige active tablets are: nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before menarche, if they have accidentally taken BRENDA-35 ED. There are no antidotes and further treatment should be symptomatic.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

BRENDA-35 ED is a progestogen-estrogen combination for the treatment of signs of androgenisation in the woman. At the same time, it is a reliable contraceptive for women who suffer primarily from these signs or in whom acne and similar conditions occur or deteriorate under the use of other ovulation inhibitors.

The substance cyproterone acetate contained in BRENDA-35 ED blocks the effect of endogenously produced and exogenously administered androgens at the target organs by means of competitive inhibition. This results in a gradual regression of signs of androgenisation, irrespective of whether increased androgen values or increased peripheral sensitivity, are the cause of the disorder. The decrease in androgen concentration at the target organs has an additional therapeutic effect.

While BRENDA-35 ED is being taken, the increased sebaceous gland function, which plays an important role in the development of acne and seborrhoea, is reduced. This leads - usually after 3 to 4 months of therapy - to the healing of existing acne efflorescences. The excessive greasiness of the hair and skin generally disappears earlier. The loss of hair which frequently accompanies seborrhoea likewise diminishes. Treatment with BRENDA-35 ED is indicated in women of child-bearing age who exhibit mild forms of hirsutism, and in particular in slightly increased facial hair; results do not, however, become apparent until after several months of use.

Apart from the described antiandrogen effect, cyproterone acetate has also a pronounced progestational action. The combination of ethinylestradiol and cyproterone acetate prevents a possible pregnancy by the inhibition of ovulation, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

As well as protection against pregnancy, combined oral contraceptives (COCs) have several positive properties which, next to the negative properties (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS and 4.8 ADVERSE EFFECTS (Undesirable effects)), can be useful in deciding on the method of birth control. For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. In addition, with the higher-dosed COCs (>35 μg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy, endometrial and ovarian cancer. These additional benefits have only been established in case control and cohort studies. Results from randomised controlled trials are not available.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Cyproterone acetate

Absorption

Following oral administration, cyproterone acetate (CPA) is completely absorbed over a wide dose range. Peak serum concentrations of 15 ng/mL are reached at about 1.6 hours after single ingestion. The absolute bioavailability of cyproterone acetate is unknown. Relative bioavailability was calculated, in a study of eight young women, from a dose-corrected comparison of area under the curves (AUC) of serum levels after 100 mg oral and 300 mg intramuscular depot administration and was found to be 80 ± 30% when averaged over all volunteers (range 23% - 119%).

Distribution

Cyproterone acetate is almost exclusively bound to serum albumin. Only 3.5 to 4.0 % of the total serum drug concentrations are present as free steroid. The ethinylestradiol-induced increase in sex hormone binding globulin (SHBG) does not influence the serum protein binding of cyproterone acetate. The apparent volume of distribution of cyproterone acetate is about 986 ± 437 L.

Metabolism

Cyproterone acetate is subject to extensive metabolism. The main metabolite in plasma was identified as 15-hydroxy-CPA which is formed possibly via the cytochrome P450 enzyme CYP3A4. The clearance rate from serum is about 3.6 mL/min/kg.

Excretion

Cyproterone acetate serum levels decrease in two phases which are characterised by half-lives of about 0.8 h and about 2.3 to 3.3 days. Cyproterone acetate is partly excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:2. The half-life of metabolite excretion is about 1.9 days.

Steady-state conditions

Cyproterone acetate pharmacokinetics are not influenced by SHBG levels. Following daily ingestion drug serum levels increase about 2.5-fold reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is rapidly and almost completely absorbed. Peak serum concentrations of about 71 pg/mL are reached within 1 to 2 hours. Absolute bioavailability, as a result of presystemic conjugation and first pass metabolism, is approximately 60%.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of approximately 5 L/kg was determined.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 mL/min/kg.

Excretion

Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterised by half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state condition

Steady state conditions are reached during the second half of a treatment cycle when serum drug levels are higher by 60% as compared to single dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is limited evidence available in the literature suggesting that estrogens may be weakly genotoxic at high doses. Ethinylestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells *in vitro)* and gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

Cyproterone acetate was negative in a standard battery of genotoxicity studies. However, further tests showed that CPA was capable of producing DNA adducts in hepatocytes in rats, dogs and monkeys *in vivo* and also in freshly isolated rat and human liver cells *in vitro* following metabolism by hydroxysteroid sulfotransferases. This DNA adduct formation occurred at exposures that might be expected to occur with the recommended dose regimen for BRENDA-35 ED.

CPA increased DNA repair activity in rat and human hepatocytes *in vitro*. CPA was clastogenic in a female rat liver micronucleus test. Other *in vivo* consequences of CPA treatment were an 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 a target for mutations. In all of these positive *in vivo* tests, hepatocyte proliferation is likely to have contributed to the results being positive.

CPA had mitogenic activity towards rat hepatocytes *in vitro*, but not human hepatocytes.

Carcinogenicity

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver.

In a long-term carcinogenicity study of CPA in rats, an increased incidence of hepatomas was reported at oral dose levels of 50 mg/kg CPA and above. In mouse (and a second rat) carcinogenicity studies, increases in benign proliferative changes (nodular hyperplasia) in liver cells of female mice and male and female rats were reported at oral doses of 2 mg/kg. Because of shortcomings in these studies (inadequate pharmacokinetic data and the need to reassess the liver pathology), the carcinogenic potential of CPA in animals could not be determined.

The clinical relevance of these findings is presently uncertain. Clinical experience and limited epidemiological data available to date do not appear to have supported an increased incidence of hepatic tumours in humans at the recommended clinical dose of 2 mg/day cyproterone acetate.

It should also be borne in mind that sexual steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each beige active tablet contains: lactose monohydrate, maize starch, povidone, magnesium stearate, sucrose, macrogol 6000, calcium carbonate, purified talc, glycerol, titanium dioxide, iron oxide yellow, glycol montanate and purified water.

Each white placebo tablet contains: lactose monohydrate, maize starch, povidone, magnesium stearate, sucrose, macrogol 6000, calcium carbonate, purified talc and glycol montanate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

BRENDA-35 ED tablets are available in PVC/Al blister packs. Each blister contains 21 beige round active tablets followed by 7 white round placebo tablets.

Each carton contains blister packs of 1 x 28 tablets or 3 x 28 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 55128 – BRENDA-35 ED tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Cyproterone acetate is a white to pale yellow crystalline powder. M.P. 206 - 213°C.

Cyproterone acetate is very soluble in chloroform and dioxane, freely soluble in acetone and benzene, soluble in ethanol, methanol and ethyl acetate, sparingly soluble in solvent hexane and almost insoluble in water.

Ethinylestradiol is a white to slightly yellowish-white, crystalline powder. M.P. 181 - 185°C.

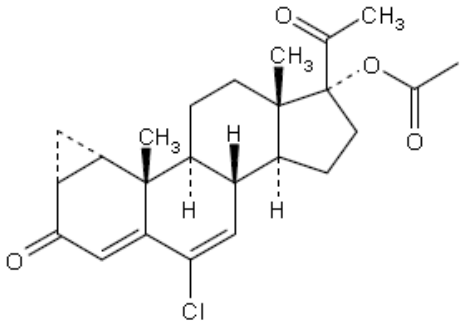
Ethinylestradiol is practically insoluble in water, freely soluble in ethanol (96%) and ether, sparingly soluble in chloroform. It dissolves in dilute alkaline solutions.

Chemical structure

Cyproterone acetate

Chemical name: 6-chloro-17α hydroxy-1α,2α-methylene-pregna-4,6-diene-3,20-dione acetate

Structural formula:



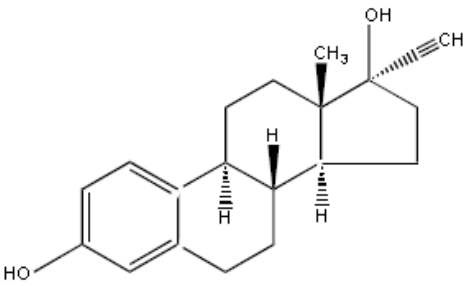
Molecular formula: $C_{24}H_{29}ClO_4$

Molecular mass: 416.96

Ethinylestradiol

Chemical name: 19-nor-17a-pregna-1,3,5,(10)-triene-20-yne-3,17β-diol

Structural formula:



Molecular formula: $C_{20}H_{24}O_2$

Molecular mass: 296.41

CAS Number

Cyproterone acetate: 427-51-0

Ethinylestradiol: 57-63-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

09/05/1996

10 DATE OF REVISION

18/02/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Correction to lactose monohydrate quantity in active tablet

BRENDA-35 ED® is a Viatris company trade mark

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