**AUSTRALIAN PRODUCT INFORMATION**

# BROOKE®

*(Drospirenone/ethinylestradiol) tablet*

## 1 NAME OF THE MEDICINE

Drospirenone / Ethinylestradiol

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg of drospirenone and 20 micrograms of ethinylestradiol as the active ingredient.

Excipients with known effect: lactose

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

## 3 PHARMACEUTICAL FORM

BROOKE ACTIVE TABLET: round, light pink, uncoated biconvex tablet with '420' debossed on one side and other side plain.

BROOKE PLACEBO TABLET: round, white to off-white, uncoated biconvex tablet with '303' debossed on one side and other side plain.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

BROOKE is indicated for use as:

- an oral contraceptive.
- treatment of moderate acne vulgaris in women who seek oral contraception
- treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control. The efficacy of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets for PMDD was not assessed beyond 3 cycles. Drospirenone 3 mg/ethinylestradiol 20 micrograms tablets has not been evaluated for treatment of PMS (premenstrual syndrome) (see **Section 5.1 PHARMACODYNAMIC PROPERTIES - CLINICAL TRIALS**).

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Combined oral contraceptives, when taken correctly, have a failure rate of approximately 1% per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. Tablet taking is continuous. One tablet is taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. A withdrawal bleed usually starts on day 2-3 after starting the placebo tablets (white tablets in the last row) and may not have finished before the next pack is started.

#### How to start BROOKE

***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). The women should be instructed to take a light pink active tablet from the green section of the pack, corresponding to that day of the week. If started on day 1 in this way, protection against pregnancy is immediate and no additional methods of contraception are required.

Starting on days 2-5 of the menstrual cycle is allowed, but during the first 7 days of the first cycle, a barrier method is recommended in addition to tablet-taking.

***Changing from another combined hormonal contraceptive (combined oral contraceptive/COC) or vaginal ring***

The woman should start with BROOKE preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. BROOKE should be started by taking a light pink active tablet from the green section of the pack.

In case a vaginal ring has been used, the woman should start taking BROOKE preferably on the day of removal of the ring, but at least when the next application would have been due.

***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 IUS on the day of its removal, or from an injectable when the next injection would be due. However, in all of these cases the woman must be advised to additionally use a barrier method for the first 7 days of tablet-taking.

***Following first-trimester abortion***

The woman may start tablet-taking immediately. When doing so, she need not take additional contraceptive measures.

***Following delivery or second-trimester abortion***

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, 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.

For breastfeeding women see **Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Lactation.**

## Management of missed tablets

Missed white pills from the last row of the blister are placebo tablets and thus can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase.

The risk of pregnancy increases with each light pink tablet missed. The following advice only refers to missed light pink active tablets:

If the woman is **less than 24 hours** late in taking any light pink 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 24 hours** late in taking any light pink active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. The placebo tablet interval for BROOKE is 4 days. Active tablet-taking must never be discontinued for longer than 7 days. Please note: BROOKE is registered in Australia for use as a contraceptive using a continuous 28 day regimen consisting of 24 active tablets followed by 4 inactive tablets; the stated efficacy in preventing pregnancy is based on this regimen.

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:

***Day 1-7***

The woman should take the last missed light pink active tablet as soon as she remembers, even if this means taking two light pink active tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days.

If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more light pink active tablets are missed and the closer they are to the white placebo tablet phase the higher the risk of a pregnancy.

***Days 8-14***

The woman should take the last missed light pink active tablet as soon as she remembers, even if this means taking two light pink 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 light pink 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 light pink active tablet, the woman should be advised to use extra precautions for 7 days.

***Day 15-24***

The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. 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 light pink 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 missed light pink active tablet as soon as she remembers, even if this means taking two light pink active tablets at the same time. She then continues to take tablets at her usual time until all the light pink active tablets are taken. The 4 white placebo tablets from the last row must be discarded. The next pack must be started right away. The user 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 4 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.

## How to delay a withdrawal bleed

Use of continuous ethinylestradiol and drospirenone without placebo tablets for up to three packs is associated with similar efficacy in terms of contraception. There is no data on the efficacy of this regimen on acne or PMDD.

During the extension period, the user may experience breakthrough bleeding or spotting. This is best managed by taking the placebo tablets to induce a withdrawal bleed than continuing active tablets. If the woman wishes to resume the 28 day dosing cycle, this may be done following the placebo tablet phase and starting a new pack.

There is no data about the long term safety of this regimen in terms of risk of VTE, endometrial safety, or cancer.

## Advice in case of gastro-intestinal disturbances

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

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets, (see above), 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

Combined hormonal contraceptives (CHCs) including BROOKE, 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 CHC 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 venous thromboembolism, 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 venous thromboembolism due to the presence of multiple risk factors

- Presence or risk of arterial thromboembolism (ATE) (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)

    - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant)
    - History of migraine with focal neurological symptoms
    - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
        - diabetes with vascular symptoms
        - severe hypertension
        - severe dyslipoproteinaemia

- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia

- Presence or history of severe hepatic disease as long as liver function values have not returned to normal

- Severe renal insufficiency or acute renal failure

- BROOKE 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)

- Undiagnosed vaginal bleeding

- Known or suspected pregnancy

- Hypersensitivity to any of the ingredients contained in BROOKE

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below are present, the benefits of BROOKE 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 BROOKE should be discontinued.

### Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives (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, multinational, cohort study (EURAS and LASS) on the safety of OC use, suggests that this increased risk is mainly present during the first 3 months.

Two prospective cohort studies (EURAS and Ingenix), each evaluating the risk of venous and arterial thromboembolism and death, were initiated separately at the time of ethinylestradiol/drospirenone 30 micrograms/3 mg approval in Europe and the United States. The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in ethinylestradiol/drospirenone 30 micrograms/3 mg users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC).

In the EURAS study, the VTE incidence rate for all OC users ranged from 8.0 to 9.9 per 10,000 WY. The overall incidence rate for past OC users was 4.7 VTE/10,000 WY, which was further specified to 19.4 VTE/10,000 WY for pregnant past OC users and 2.3 VTE/10,000 WY for non-pregnant past OC users. The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in ethinylestradiol/drospirenone 30 micrograms/3 mg users compared to users of other COCs, including those containing levonorgestrel. In this second study, COC comparator groups were selected based on them having similar characteristics to those being prescribed ethinylestradiol/drospirenone 30 micrograms/3 mg.

Another large population-based study (Heit et al) found an incidence rate of 20 VTE/10,000 WY in pregnant or postpartal women and 4.6 in non-pregnant women of reproductive age. All of these rates tend to be higher than those reported in the past.

Based on this data it can be assumed that the VTE risk in users of OC users is roughly twice as high for non-pregnant non-OC users. The absolute attributable risk (approximately 4 VTEs per 10,000 WY of use) was found to be slightly higher in these studies than reported in the past. Nevertheless, the risk in OC users remains lower than the VTE risk associated with pregnancy and the first weeks following delivery.

Two additional epidemiological studies, one case control study (van Hylckama Vlieg et al.) and one retrospective cohort study (Lidegaard et al., 2009) suggested that the risk of venous thromboembolism occurring in ethinylestradiol/drospirenone 30 micrograms/3 mg users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so called third generation COCs). In the case- control study, however, the number of ethinylestradiol/drospirenone 30 micrograms/3 mg cases was very small (1.2% of all cases making the risk estimates unreliable). The relative risk for ethinylestradiol/drospirenone 30 micrograms/3 mg users in the retrospective cohort study was greater than that for users of other COC products when considering women

who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the products for 1 to 4 years, the relative risk was similar for users of ethinylestradiol/drospirenone 30 micrograms/3 mg to that of other COC products.

Two further retrospective database studies (Parkin et al., Jick and Hernandez) published in 2011, suggested a greater risk for VTE in users of drospirenone-containing COCs compared to levonorgestrel-containing COCs. However, the number of drospirenone cases in the Parkin et al. study was very small.

It is important that women understand that VTE associated with CHC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with CHC use.

Drospirenone containing COCs may be associated with a higher risk of VTE than COCs containing the progestogen levonorgestrel or some other progestogens. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase.

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

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting BROOKE (See **Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy and Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in 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, cerebral 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).

BROOKE 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 (venous thromboembolism 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 BROOKE (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 BROOKE 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 venous thromboembolism.

***Symptoms of VTE (deep vein thrombosis and pulmonary embolism)***

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 deep vein thrombosis (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 pulmonary embolism (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 non-specific 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 discolouration 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 arterial thromboembolism (e.g. myocardial infarction, 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. BROOKE 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 (arterial thromboembolism 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
  - 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.

***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 a 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 myocardial infarction (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 may have a fatal outcome.

## Other Conditions

Potassium excretion capacity may be limited in patients with renal insufficiency. In a clinical study, drospirenone intake did not show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalaemia can be assumed only for patients whose pre-treatment serum potassium is in the upper reference range, and who are additionally using potassium sparing medicines.

Women with hypertriglyceridemia, 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. The antimineralocorticoid effect of drospirenone may counteract ethinylestradiol-induced increases in blood pressure observed in normotensive women taking other combined oral contraceptives. 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; otosclerosis-related hearing loss.

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

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 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 diabetics taking low dose COCs (containing < 50 µg ethinylestradiol). However, diabetic women 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.

Each light pink active tablet contains 72.14 mg of lactose and each white placebo tablet contains 98.50 mg of lactose. 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 COC use, guided by the contraindications and warnings, and should be repeated at least annually during the use of COCs. 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 Acquired Immune Deficiency Syndrome (AIDS)

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible infections (STIs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

### Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed light pink active tablets, gastrointestinal disturbances during active tablet taking or concomitant medication (see **Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**). The more light pink active tablets are missed and the closer they are to the white placebo tablet phase, the higher the risk of a pregnancy.

### 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 prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

In women who choose to use BROOKE with a continuous regimen, withdrawal bleeding is not expected to occur during the extension period when active tablet taking is uninterrupted. Therefore, the absence of withdrawal bleeding cannot be used as a sign of an unexpected pregnancy and as such, unexpected pregnancy may be difficult to recognise. This may be of particular importance to women using teratogenic drugs. Although pregnancy is unlikely if BROOKE is taken as directed, if for any reason, pregnancy is suspected, a pregnancy test should be performed.

### 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

BROOKE is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see **Section 4.3 CONTRAINDICATIONS**).

### Use in Renal Impairment

BROOKE is contraindicated in women with severe renal insufficiency or acute renal failure (see **Section 4.3 CONTRAINDICATIONS**).

### Use in the Elderly

BROOKE is not indicated after menopause.

### Paediatric Use

BROOKE is only indicated after menarche.

### Effects on Laboratory Tests

The use of contraceptive steroids 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. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

### Effects of Other Medicines on BROOKE

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 oral 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 the COC 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 in which the barrier method is used runs beyond the end of the active tablets in the COC pack, the white placebo tablets should be omitted and the next COC pack started.

- **Substances increasing the clearance of COCs (diminished efficacy of COCs 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 COCs**

  When co-administered with COCs, many HIV/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations 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 by 1.4 to 1.6-fold respectively, when taken concomitantly with a COC containing 35 μg ethinylestradiol.

### Effects of COCs on Other Medicines

COCs may affect the metabolism of certain other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Based on *in vitro* inhibition studies and *in vivo* interaction studies in female volunteers taking omeprazole, simvastatin or midazolam as a marker substrates, an interaction of drospirenone at doses of 3 mg, with the cytochrome P450 mediated metabolism of other medicines is unlikely.

In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol led to no or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase in CYP1A2 substrates.

### 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.

### Other Interactions

There is a theoretical potential for an increase in serum potassium in women taking drospirenone 3 mg/ethinylestradiol 20 micrograms tablets with other medicines that may increase serum potassium levels. Such medicines include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indometacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on Fertility

No data available.

### Use in Pregnancy

Pregnancy Category: B3

(Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human

fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.)

Drospirenone and/or its metabolites crossed the placenta and entered the foetus when administered orally to pregnant rats and rabbits. Treatment of pregnant rats with a combination of drospirenone and ethinylestradiol resulted in a dose-dependent increased incidence of embryolethality due to increased pre- and post-implantation losses. There was no indication of teratogenic effects of drospirenone in rats or rabbits.

Dose-dependent feminisation of male foetuses and virilisation of female foetuses were seen following administration of a combination of drospirenone and ethinylestradiol to female rats in the last third of pregnancy. Feminising effects in male foetuses were consistent with drospirenone's anti-androgenic activity and were observed at an estimated systemic exposure approximately 8-13 fold than that anticipated clinically (based on AUC). Virilisation of female foetuses was seen following systemic drospirenone exposure of approximately 2 to 5-fold than that anticipated clinically (based on AUC). This effect has previously been described for estrogens in rats. When pregnant monkeys received a combination of drospirenone and ethinylestradiol by daily oral administration during the major period of organogenesis and sexual organ differentiation, abortion rates were increased in a dose-dependent manner. However, there were no indications of teratogenicity.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who take COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. Drospirenone 3 mg/ethinylestradiol 20 micrograms tablet is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of BROOKE, the preparation must be discontinued immediately (see also **Section 4.3 CONTRAINDICATIONS**).

### Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in the milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

## 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)

The most serious adverse reactions associated with the use of oral contraceptives are indicated under **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** (see also **Section 4.3 CONTRAINDICATIONS**).

### Clinical trial data

Adverse drug reactions which have been associated with the use of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets as an oral contraceptive or in the treatment of moderate acne vulgaris are listed below.

| System Organ Class | Common (≥ 1/100 to < 1/10) | Uncommon (≥ 1/1,000 to < 1/100) | Rare (≥ 1/10,000 to < 1/1,000) |
|---|---|---|---|
| **Infections and infestations** | | | Candidiasis |
| **Blood and lymphatic system disorders** | | | Anaemia<br>Thrombocythemia |
| **Immune system disorders** | | | Allergic reaction |
| **Endocrine disorders** | | | Endocrine disorder |
| **Metabolism and nutrition disorders** | | | Increased appetite<br>Anorexia |

| | | | |
|---|---|---|---|
| | | | Hyperkalaemia<br>Hyponatraemia |
| **Psychiatric disorders** | Emotional lability<br>Depression/ depressive mood | Decrease and loss of libido<br>Nervousness<br>Somnolence | Anorgasmia<br>Insomnia |
| **Nervous system disorders** | Headache<br>Migraine | Dizziness<br>Paresthesia | Vertigo<br>Tremor |
| **Eye disorders** | | | Conjunctivitis<br>Dry eye<br>Eye disorder |
| **Cardiac disorders** | | | Tachycardia |
| **Vascular disorders** | | Varicose vein<br>Hypertension | Phlebitis<br>Vascular disorders<br>Venous and arterial thromboembolic events**<br>Epistaxis<br>Syncope |
| **Gastrointestinal disorders** | Nausea | Abdominal pain<br>Vomiting<br>Dyspepsia<br>Flatulence<br>Gastritis<br>Diarrhoea | Enlarged abdomen<br>Gastrointestinal disorder<br>Gastrointestinal fullness<br>Hiatus hernia<br>Oral candidiasis<br>Constipation<br>Dry mouth |
| **Hepatobiliary disorders** | | | Biliary pain<br>Cholecystitis |
| **Skin and subcutaneous tissue disorders** | | Acne<br>Pruritus<br>Rash | Chloasma<br>Eczema<br>Alopecia<br>Dermatitis acneiform<br>Dry skin<br>Erythema nodosum<br>Hypertrichosis<br>Skin disorder<br>Skin striae<br>Contact dermatitis<br>Photosensitive dermatitis<br>Skin nodule |
| **Musculoskeletal and connective tissue disorders** | | Back pain<br>Pain in extremity<br>Muscle cramps | |
| **Reproductive system and breast disorders** | Breast pain<br>Unscheduled uterine/Genital tract bleeding not further specified*<br>Metrorrhagia<br>Amenorrhoea | Vaginal candidiasis<br>Pelvic pain<br>Breast enlargement<br>Fibrocystic breast<br>Genital discharge<br>Hot flushes<br>Vaginitis<br>Menstrual disorder<br>Dysmenorrhea<br>Hypomenorrhea<br>Menorrhagia<br>Vaginal dryness<br>Papanicolaou smear suspicious | Dyspareunia<br>Vulvovaginitis<br>Postcoital bleeding<br>Withdrawal bleeding<br>Breast cyst<br>Breast hyperplasia<br>Breast neoplasm<br>Cervical polyp<br>Endometrial atrophy<br>Ovarian cyst<br>Uterine enlargement |
| **General disorders and administration site conditions** | | Asthenia<br>Increase sweating<br>Oedema<br>(Generalised oedema, Peripheral oedema, Face oedema) | Malaise |
| **Investigations** | | Weight increase | Weight decrease |

*Bleeding irregularities usually subside during continued treatment.

** Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. Frequency was borderline to Very Rare. Venous and arterial thromboembolic events summarises the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as haemorrhagic.

In addition, the following undesirable effects have been reported in users of COCs and the association has been neither confirmed nor refuted:

Common: breast tenderness

Uncommon: breast hypertrophy, fluid retention

Rare: vaginal discharge, breast discharge, contact lens intolerance.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Erythema multiforme has been reported in post marketing surveillance. The frequency cannot be estimated from the available data and is therefore unknown.

### 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 has not yet been any clinical experience of overdose with drospirenone 3 mg/ethinylestradiol 20 micrograms tablets. On the basis of general experience with COCs, symptoms that may occur in case of overdose of active tablets are: nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product. 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

The contraceptive effect of combined oral contraceptives is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, combined oral contraceptives have several positive properties which, next to the negative properties (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))**, can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Drospirenone has antimineralocorticoid activity, counteracting estrogen-related sodium retention. In combination with ethinylestradiol, drospirenone displays a favourable lipid profile with an increase in high density lipoprotein (HDL). Drospirenone exerts antiandrogenic activity. Drospirenone does not counteract the

ethinylestradiol-related sex hormone binding globulin (SHBG) increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. This, in combination with the antimineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone. Apart from this, with the higher-dosed Combined Oral Contraceptives (COCs) (50 micrograms ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed combined oral contraceptives such as drospirenone 3 mg/ethinylestradiol 20 micrograms tablets remains to be confirmed.

## Clinical Trials

***Contraception***

Study A12007 and Study A30713 were both large multi-centre open trials evaluating contraceptive efficacy of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets in 1027 and 1101 women respectively over 13 cycles. The age range was 17 to 36 years. The BMI in these studies ranged from 17 to 37.6 kg/$m^2$ with mean values of 22.4 (A12007) and 21.7 (A30713) respectively. The primary efficacy variable was the number of unintended pregnancies (Pearl Index). The Pearl Index (PI) is defined as the number of pregnancies divided by the exposure time in woman years (WY) multiplied by 100. Pregnancies attributed to non-compliant use of the contraceptive were considered patient failure; all other pregnancies were considered method failure. In Study A12007 the PI was 1.29 with an upper two-sided 95% confidence interval of 2.30. When corrected to exclude patient failure the PI was 0.72 with an upper two-sided 95% confidence interval of 1.69. In Study A30713, the PI was 0.49 with an upper two-sided 95% confidence interval of 1.14. When corrected to exclude patient failure the PI was 0.22 with an upper two-sided 95% confidence interval of 0.80.

Study A29551 was a multi-centre open randomised study to investigate the bleeding pattern, cycle control, contraceptive reliability and general safety of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets in 229 women compared to ethinylestradiol 0.02 mg + desogestrel 0.15 mg in 220 women taken for 21 days followed by pill free interval of 7-days over 7 cycles. There were no pregnancies in the group taking drospirenone 3 mg/ethinylestradiol 20 micrograms tablets which lead to a Pearl Index of 0 with an upper two-sided 95% confidence interval of 3.40 and 3.55 for the Pearl Index and corrected index respectively.

A small fourth study (A09151) evaluated lipid and haemostatic and carbohydrate parameters in 29 women taking drospirenone 3 mg/ethinylestradiol 20 micrograms tablets compared to ethinylestradiol 0.02 mg + desogestrel 0.15 mg in 30 women taken for 21 days followed by pill free interval of 7-days over 7 cycles. No significant differences in any of the lipid, haemostatic, or carbohydrate parameters were observed between the two treatments.

The Pearl Index from the integrated efficacy analysis from these 4 studies was 0.80 with an upper two-sided 95% confidence interval of 1.30. When corrected to exclude patient failure the Pearl Index, was 0.41 with an upper two-sided 95% confidence interval of 0.85.

The Pearl Index for drospirenone 3 mg/ethinylestradiol 20 micrograms tablets was calculated from data from studies in which the protocol allowed up to 24 hours delay in pill taking without a requirement for additional contraception, and in which the regimen was 24 active pills and 4 inactive pills taken sequentially over 28 days per cycle.

The parameters of bleeding pattern and cycle control demonstrated a well-controlled and regular bleeding sequence for drospirenone 3 mg/ethinylestradiol 20 micrograms tablets as compared to the comparator used. No clinically relevant changes in blood pressure or weight were observed. Irrespective of treatment duration, the mean absolute change in body weight at the final examination was –0.1 kg and the mean maximum increase in body weight versus baseline was 1.2 kg (n=1,319). The mean maximum decrease was 1.6 kg. The majority of women treated with drospirenone 3 mg/ethinylestradiol 20 micrograms tablets were satisfied or very satisfied with the treatment and reported no change or improvement in their physical or emotional well-being. The overall subjective assessment of women treated with drospirenone 3 mg/ethinylestradiol 20 micrograms

tablets was equivalent to the comparator group.

***Acne***

Drospirenone 3 mg/ethinylestradiol 20 micrograms tablets as an acne therapy was evaluated in two pivotal multi-centre, double blind, randomised placebo-controlled studies of 6 month duration. A total of 451 drospirenone 3 mg/ethinylestradiol 20 micrograms subjects and 442 placebo subjects were included in the final integrated analysis. Patients had moderate acne defined in the protocol as a minimum of 40 lesions (i.e. at least 20 inflammatory lesions and at least 20 non-inflammatory lesions) and were between ages of 14 to 45. The primary efficacy endpoints were the percent change in total lesions, inflammatory lesions, non-inflammatory lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) on day 15 of cycle 6. The results for the primary efficacy variables are provided in Table 1 below:

**Table 1: Results for the Acne primary efficacy variables in two pivotal multicentre studies**

| | **Drospirenone 3 mg/ ethinylestradiol 20 micrograms (n=451)** | **Placebo (n=442)** | **Difference** | ***p*-value** |
|---|---|---|---|---|
| **Mean change in Total Lesion Count (%)** | -45.3 | -29.1 | -16.1 | <0.0001 |
| **Mean change in Inflammatory Lesion Count (%)** | -50.3 | -34.9 | -15.3 | <0.0001 |
| **Mean Change in Non-Inflammatory Lesion Count (%)** | -41.3 | -23.2 | -18.1 | <0.0001 |
| **ISGA Success (Percent of Subjects rated "Clear" or "Almost Clear")** | 18.6 | 6.8 | Odds Ratio 3.413 (2.146, 5.426 95% C.I.) | <0.0001 |

In addition, there was a statistical difference ($p$ = <0.0001) in the percentage of patients considered improved at the final assessment by the investigator for drospirenone 3 mg/ethinylestradiol 20 micrograms tablets (87.6%) as compared to placebo (66.0%) [odds ratio; 3.83 95% CI 2.58, 5.80].

***Premenstrual Dysphoric Disorder (PMDD)***

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses. The disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Two multi-centre, double-blind, randomised, placebo-controlled studies were conducted to evaluate the effectiveness of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets in treating the symptoms of PMDD. Women aged 18-42, > 1 year after menarche with no known contraindications for oral contraceptives and who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Subjects with past or present psychiatric disorders other than PMDD were excluded. Both studies measured the treatment effect of drospirenone 3 mg/ethinylestradiol 20 micrograms tablets using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-

aged women with PMDD who were randomly assigned to receive drospirenone 3 mg/ethinylestradiol 20 micrograms tablets or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrolment difficulties. In the supportive study, a total of 64 women of reproductive age with PMDD were treated initially with drospirenone 3 mg/ethinylestradiol 20 micrograms tablets or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems (DRSP). Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received drospirenone 3 mg/ethinylestradiol 20 micrograms tablets had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking drospirenone 3 mg/ethinylestradiol 20 micrograms tablets, compared to 30.0 points in women taking placebo in the full analysis set. The difference between treatment groups (-7.5) was statistically significant (p=0.0001). In the supportive study, the average decrease from baseline for drospirenone 3 mg/ethinylestradiol 20 micrograms tablets (n=42) was -22.9, compared to -10.5 in women (n=41) taking placebo (p= 0.0001; difference - 12.47; 95% CI: -18.28, -6.66).

A statistical comparison between the treatments for the efficacy variables (full analysis set) in the PMDD Pivotal Study are presented in Table 2 below.

**Table 2: Statistical comparison between the treatments for the efficacy variables in the PMDD Pivotal Study**

| | **Drospirenone 3 mg/ ethinylestradiol 20 micrograms** | | **Placebo** | | **Difference (95% CI)** | ***p*-value** |
|---|---|---|---|---|---|---|
| | **n** | **Adjusted Mean Change from Baseline** | **n** | **Adjusted Mean Change from Baseline** | | |
| **Primary Endpoint** | | | | | | |
| DRSP (1st 21 items) | 190 | -37.49 | 194 | -29.99 | -7.5 (-11.20, -3.80) | 0.0001 |
| **Secondary Endpoints** | | | | | | |
| DRSP (Item 22)[1] | 189 | -1.98 | 194 | -1.64 | -0.33 (-0.55, -0.12) | 0.0022 |
| DRSP (Item 23)[2] | 189 | -1.94 | 194 | -1.61 | -0.34 (-0.55, -0.12) | 0.0020 |
| DRSP (Item 24)[3] | 189 | -2.10 | 194 | -1.68 | -0.42 (-0.64, -0.20) | 0.0002 |
| CGI[4] Illness Severity | 209 | -1.57 | 193 | -1.36 | -0.22 | 0.1110 |
| CGI Efficacy Index | 213 | 2.07[5] | 196 | 2.10[5] | -0.03 | 0.8297 |
| CGI Global Improvement - Observer | 212 | 2.21[6] | 198 | 2.51[6] | -0.30 | 0.0199 |
| CGI Global Improvement – Self rated | 213 | 2.27[6] | 202 | 2.53[6] | -0.26 | 0.0573 (0.0137)[7] |
| SF-36[8] Mental health | 200 | 10.15 | 186 | 8.33 | 1.82 | 0.1252 |
| SF-36[8] Physical health | 200 | 1.62 | 186 | 1.54 | 0.08 | 0.9247 |
| Endicotts QoL + Satisfaction[9] (1st 14 items) | 200 | 19.56 | 187 | 16.69 | 2.87 (-0.02, 5.77) | 0.0519 |
| Endicotts QoL + Satisfaction Item 16[10] | 197 | 1.18 | 184 | 1.07 | 0.12 (-0.08, 0.31) | 0.2429 |
| PMS symptoms rating scales - Observer | 200 | -12.34 | 187 | -10.42 | -1.92 (-3.79, -0.05) | 0.0446 |
| PMS symptoms rating scales - Self rated | 201 | -16.76 | 186 | -13.28 | -3.49 (-5.71, -1.26) | 0.0022 |

**Table Notes:**

1. Item 22 - Reduction of productivity or inefficiency at work, home or school
2. Item 23 - Interference with hobbies or social activities

3. Item 24 - Interference with relationships
4. Clinical Global Impressions
5. Treatment rating on efficacy index scale. Scores range from 0.25 to 4 with higher scores indicating therapeutic improvements with minimal side effects.
6. Subject improvement scores. The degrees of subject improvement were rated on scale of 1 (very much improved) to 7 (very much worse). Lower scores indicate improvement.
7. *p*-value from rank ANOVA, computed if Shapiro-Wilk normality test was significant at the 0.05 level
8. Self-rated quality of life survey
9. Assessed degree of enjoyment and satisfaction experienced during the week prior to menses
10. Item 16 – overall life satisfaction and contentment

## 5.2 PHARMACOKINETIC PROPERTIES

The impact of ethnic factors on the pharmacokinetics of drospirenone and ethinylestradiol was studied after single and repeated daily oral administration to young healthy Caucasian and Japanese women. The results showed that ethnic differences between Japanese and Caucasian women had no clinically relevant influence on the pharmacokinetics of drospirenone and ethinylestradiol.

### Drospirenone

#### *Absorption*

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the drug in serum of about 35 ng/mL are reached at approximately 1-2 h after single ingestion. Bioavailability is between 76 and 85%. The intake of food had no influence on the extent of absorption but the maximum concentration was reduced as compared to drug intake on an empty stomach.

#### *Distribution*

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of 1.6 ± 0.7 h and 27.0 ± 7.5 h, respectively. Drospirenone is bound to serum albumin and does not bind to SHBG or corticoid binding globulin (CBG). Only 3 - 5% of the total serum drug concentrations are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 L/kg.

#### *Metabolism*

Drospirenone is extensively metabolised after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalysed by cytochrome P450 3A4 and has demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19 *in vitro*.

#### *Excretion*

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 mL/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and faeces is approximately 40 h.

#### *Steady-State Conditions*

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/mL are reached between day 7 and day 14 of treatment. Serum drospirenone levels accumulated by a factor of about 2 to 3 as a consequence of the ratio of terminal half- life and dosing interval. Further accumulation of drospirenone levels beyond treatment cycles was observed between cycles 1 and 6 but thereafter, no further accumulation was observed.

## Special Populations

### *Effect of renal impairment*

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance $CL_{cr}$, 50-80 mL/min) were comparable to those of women with normal renal function ($CL_{cr}$, > 80mL/min). The serum drospirenone levels were on average 37% higher in women with moderate renal impairment ($CL_{cr}$, 30-50 mL/min) compared to those in women with normal renal function. Drospirenone treatment was well tolerated by all groups.

Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

### *Effect of hepatic impairment*

In women with moderate impairment of hepatic function (Child-Pugh B) mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases with similar $C_{max}$ values. The mean terminal half-life of drospirenone for the volunteers with moderate hepatic impairment was 1.8 times greater than for the volunteers with normal hepatic function.

About 50% decrease in apparent oral clearance (CL/F) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers. Even in the presence of diabetes and concomitant treatment with spironolactone (2 factors that can predispose a patient to hyperkaelemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child- Pugh B).

## Ethinylestradiol

### *Absorption*

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of approximately 88 to 100 pg/mL are reached within 1 - 2 hours after single oral administration. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%. Concomitant intake of food had a variable effect. The maximum concentration was reduced in all subjects and the bioavailability of ethinylestradiol was reduced in about 25% of the investigated subjects.

### *Distribution*

Serum ethinylestradiol levels decrease in two phases; the terminal disposition phase is characterised by a half-life of approximately 24 hours. 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 of ethinylestradiol is approximately 5 mL/min/kg.

### *Excretion*

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

***Steady-State Conditions***

Steady-state conditions are reached during the second half of a treatment cycle and serum levels of ethinylestradiol accumulate by a factor of about 1.4 to 2.1.

## 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 *in vitro* (clastogenic effects were not consistently seen and occurred at high concentrations). *In vivo* studies did not confirm these results.

Drospirenone was found to induce chromosome aberrations in human peripheral lymphocytes. However, drospirenone was not mutagenic in bacterial and mammalian cell gene mutation assays *in vitro* and was not clastogenic in mouse micronucleus assays *in vivo*. Interactions between drospirenone and the DNA of liver cells which indicate a genotoxic potential were found in *in vitro* and *in vivo* studies in rats. No such finding was observed in human liver cells *in vitro*.

### Carcinogenicity

Long-term carcinogenicity studies were performed in mice and rats with drospirenone, ethinylestradiol and with a combination of both products. After 2 years oral treatment of mice and rats with drospirenone alone, there were no increases in the incidence of neoplastic lesions. Exposure to drospirenone (based on AUC) was up to 3-fold (mice) and 8-fold (rats) than that anticipated in humans at the recommended clinical dose. In contrast, treatment with the combination of drospirenone and ethinylestradiol resulted in an increased rate of neoplastic lesions in the mammary glands and uteri of mice and rats and in the pituitary glands of mice. The tumour pattern was similar but the incidence increased even further in animals receiving ethinylestradiol alone, indicating that ethinylestradiol was responsible for the increase in neoplastic lesions. Co-administration of drospirenone decreased the carcinogenic potential of ethinylestradiol in the mouse pituitary and in the mouse and rat uterus and mammary gland.

The ethinylestradiol-induced tumours in rodents have previously been seen with other ethinylestradiol-containing products and are considered attributable to species-specific effects of estrogens on prolactin secretion in rodents.

Although, long-term animal studies did not definitively indicate a tumourigenic potential for the clinical use of either drospirenone or ethinylestradiol, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Each light pink active tablet contains contain the following excipients: lactose monohydrate, maize starch, crospovidone, povidone, magnesium stearate and iron oxide red.

Each white placebo tablet contains: lactose monohydrate, polacrilin potassium and magnesium stearate.

## 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. Store in original container.

## 6.5 NATURE AND CONTENTS OF CONTAINER

BROOKE tablets are contained in PVDC/PVC/Aluminium foil blister packs. The blister strips are contained within a tri-laminated foil pouch. Each blister contains 24 light pink tablets followed by 4 white placebo tablets.

Each carton contains memo packs of 1x28, 2x28, 3x28, 4x28 or 6x28 tablets.

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

### Australian Register of Therapeutic Goods (ARTG)

AUST R 219081 – BROOKE drospirenone/ethinyloestradiol 3 mg/20 microgram tablet blister composite pack

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

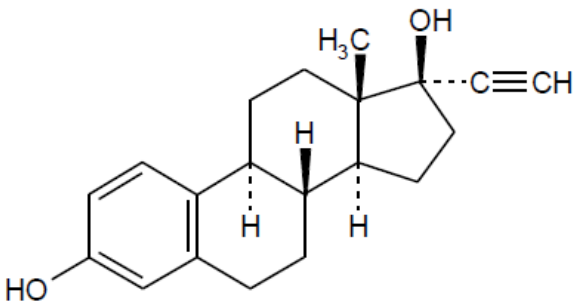
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical Structure**

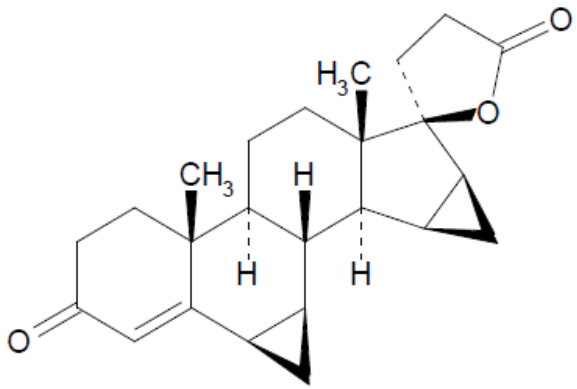
BROOKE is a combined oral contraceptive tablet containing the synthetic progestogen, drospirenone and the synthetic estrogen, ethinylestradiol.

Ethinylestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides. The chemical name for ethinylestradiol is 3-Oxo-6α,7α,15α,16α-tetrahydro-3´H,3˝H-dicyclopropa-[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone and has the following structural formula:




Molecular Formula: $C_{20}H_{24}O_2$ Molecular Weight: 296.41

Drospirenone is a white to off-white crystalline powder. It is freely soluble in methylene chloride, soluble in acetone, methanol, sparingly soluble in ethylacetate and ethanol 96% (v/v) and practically insoluble in hexane and water. The chemical name for drospirenone is 6β,7β,15β,16β-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone and has the following structural formula:




Molecular formula: $C_{24}H_{30}O_3$ Molecular weight: 366.50

**CAS Number**

Ethinylestradiol CAS Registry No: 57-63-6

Drospirenone CAS Registry No: 67392-87-4

# 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

24/05/2022

# 10 DATE OF REVISION

04/07/2023

**Summary Table of Changes**

| Section Changed | Summary of New Information |
|---|---|
| **ALL** | Minor editorial change |
| **4.2** | 'How to delay a period' section updated |
| **4.3** | Addition of contraindications |
| **4.4** | 'Reduce Cycle Control' section updated to include information regarding withdrawal bleeding in women who choose to delay a period<br>Addition of warnings and precautions |

| | |
|---|---|
| **4.5** | Addition of interactions |
| **4.7** | Addition of precautions |
| **4.8** | Reclassification of adverse effect “migraine” from vascular disorders to nervous system disorders |
| **4.9** | Update to include information related to withdrawal bleeding |
| **5.2** | Update to include information related to Drospirenone metabolism |
| **4.3, 4.4, 4.5** | Update to ethinylestradiol interaction with hepatitis C antivirals and the risk of liver function test elevations |



**BROOKE_pi\Jul23/01**