# NEW ZEALAND DATA SHEET

# BROOKE

## 1. Product Name

BROOKE , drospirenone 3 mg and ethinylestradiol 20 micrograms, tablet.

## 2. Qualitative and Quantitative Composition

Each blister strip holds 24 active hormonal tablets and 4 non-hormonal tablets. Each active hormonal tablet contains 3 mg drospirenone and 20 micrograms of ethinylestradiol.

Excipient(s) with known effect

BROOKE contains lactose.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

Active hormonal tablets: round, light pink, uncoated biconvex tablets debossed with '420' on one side and plain on the other side.

Non-hormonal tablets: round, white to off-white, uncoated, biconvex placebo tablets with '303' debossed on one side and plain on the other.

## 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 BROOKE for PMDD was not assessed beyond 3 cycles. BROOKE has not been evaluated for treatment of PMS (premenstrual syndrome), see section 5.1.

### *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. Withdrawal bleeding 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 woman should be instructed to take a 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 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

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

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 pink active tablet from the green section of the pack. In case a vaginal ring or transdermal patch has been used, the woman should start using BROOKE preferably on the day of removal, 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 any day from the minipill (or from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

**Following first-trimester abortion**

The woman may start 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

## 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 following advice only refers to missed 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 she 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. Active tablet-taking must never be discontinued for longer than 7 days (please note the recommended placebo tablet interval is 4 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:

*Day 1 - 7*

The woman should take the last missed tablet as soon as she remembers, even if this means taking two 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 tablets that are missed and the closer they are to the placebo tablet phase the higher the risk of a pregnancy.

*Days 8 - 14*

The woman should take the last missed tablet as soon as she remembers, even if this means taking two 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 tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra contraceptive 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 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 tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until all the active tablets are used up. The 4 white tablets from the last row (placebo tablets) 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 first normal tablet-free interval, the possibility of a pregnancy should be considered.

### How to delay a period

To delay a period the woman should continue with another pack of BROOKE without taking the placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the active tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of BROOKE is then resumed after the placebo tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

### 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 - 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 has to take the extra tablet(s) needed from another pack.

## *4.3 Contraindications*

Combined oral contraceptives (COCs) 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 COC use, the product should be stopped immediately.

Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.

- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.

- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see section 4.4).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- 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.
- 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 the active substances or to any of the excipients listed in section 6.1.

## *4.4 Special warnings and precautions for use*

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

### Circulatory disorders

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk for VTE is highest during the first year a woman takes a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) with the same or a different COC. Data from a large, prospective multinational, cohort study on the safety of COC use suggests that this increased risk is mainly present during the first 3 months.

Presently available information on drospirenone COCs suggests that drospirenone 30 µg containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progesterone levonorgestrel. However epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase.

A number of studies have compared the risk of VTE for users of ethinyloestradiol/drospirenone 30 µg/3 mg to the risk for users of other COCs, including COCs containing levonorgestrel.

Epidemiological studies have suggested that the incidence of VTE in women with no known risk factors for VTE who take low dose oestrogen (< 50 micrograms ethinylestradiol) COCs ranges from about 20 cases per 100,000 woman-years (for COCs containing levonorgestrel) to 40 cases per 100,000 woman-years (for COCs containing desogestrel or gestodene). This compared with 5 - 10 cases per 100,000 woman-years for non-users and 60 cases per 100,000 pregnancies.A large (approximately 140,000 women years (WY) of observation), prospective, multinational, cohort study

on the safety of OC use showed the risk of VTE in users of COCs containing drospirenone to be comparable to that of those containing levonorgestrel (second-generation). A further prospective cohort study showed a comparable risk of thrombosis in users of COCs containing drospirenone and other COC users, including levonorgestrel. For details see the following table from the multinational cohort study:

**Incidences[+] (with 95% Confidence Interval) of thromboembolic events in the multinational cohort study[#]**

| Type of event | D+EE[@] (28,621 WY) | | LNG-containing (31,415 WY) | | Other OCs (52,623 WY) | |
|---|---|---|---|---|---|---|
| | Incidence + | 95% CI | Incidence + | 95% CI | Incidence + | 95% CI |
| **VTE* & ATE** combined** | 9.8 | 6.5 – 14.1 | 10.8 | 7.5 – 15.1 | 11.6 | 8.9 – 14.9 |
| **VTE* only** | 9.1 | 5.9 – 13.3 | 8.0 | 5.2 – 11.7 | 9.9 | 7.4 – 13.0 |
| **ATE** only** | 0.7 | 0.1 – 2.5 | 2.9 | 1.3 – 5.4 | 1.7 | 0.8 – 3.2 |
| **All cause mortality** | 1.4 | 0.4 – 3.6 | 2.5 | 1.1 – 5.0 | 1.7 | 0.8 – 3.2 |

@ D+EE = drosperinone 3 mg + ethinylestradiol 30 micrograms
+ Incidence is given in events per 10,000 Women Years (WY)
* Venous-thromboembolic Events (VTE) comprises Deep Vein Thromboses and Pulmonary Embolism
** Arterial thromboembolic Events (ATE) comprises Cerebral Vascular Accident and Acute Myocardial Infarction
# Final study results: April 2006

Two additional epidemiological studies, one case control study and one retrospective cohort study suggested that the risk of venous thromboembolism occurring in ethinylestradiol 30 micrograms/drospirenone 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 30 micrograms/drospirenone 3 mg cases was very small (1.2% of all cases making the risk estimates unreliable). The relative risk for ethinylestradiol 30 micrograms/drospirenone 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 30 micrograms/drospirenone 3 mg to that of other COC products. In 2011 a re-analysis of the retrospective cohort study estimated the VTE risk of users of drospirenone 30 µg to be approximately twice that of users of levonorgestrel. However, the re-analysis was also affected by some of the same flaws as the original analysis such as lacking validation of VTE diagnosis. It also contained substantial inconsistencies compared to the original study with regard to the duration of use effect.

Another retrospective cohort study reported a higher risk of VTE when comparing drospirenone 30 µg to levonorgestrel COCs, however, the study had some methodological deficiencies, such as incomplete outcome validation, sociodemographic differences between the study populations, inability to account for some important confounding factors.

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 other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. Symptoms of venous (includes PE and DVT) or arterial thrombotic/thromboembolic (includes MI, vascular occlusion and cerebrovascular accident) events can include: unilateral leg pain and/or swelling; 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; sudden, severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe, prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen, fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment (see section 4.3).

The risk of venous or arterial thrombotic/thromboembolic event or of a cerebrovascular accident increases with:

- age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
- obesity (body mass index over 30 kg/$m^2$);
- overweight;
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation (e.g. long haul flights), major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low dose COCs (< 50 µg ethinylestradiol).

## Tumours

The most important risk factor for cervical cancer is persistent 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 using 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 drugs.

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using 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 using other combined oral contraceptives. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician 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 oestrogens 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 using 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 78.8 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 Immuno 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 DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES).

### 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.

### Carcinogenicity and mutagenicity

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) 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 oestrogens 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.

### Genotoxicity

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.*

### Paediatric use

BROOKE is only indicated after menarche. There is no data suggesting the need for a dosage adjustment.

### Use in the elderly

BROOKE is not indicated after menopause.

### Patients with hepatic impairment

BROOKE is contraindicated in women with severe hepatic diseases. See CONTRAINDICATIONS.

### Patients with renal impairment

BROOKE is contraindicated in women with severe renal insufficiency or acute renal failure. See CONTRAINDICATIONS.

### Effect 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 antimineralocorticoid activity.

## *4.5 Interaction with other medicines and other forms of interaction*

### 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.

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 be 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 oestrogen or progestogen. These changes may be clinically relevant in some cases.

***Antibiotics (interference with enterohepatic circulation)***

Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic agents (e.g. penicillins, tetracyclines) are given, which may reduce ethinyloestradiol concentrations.

Women prescribed antibiotics (except rifampicin or griseofulvin) should use a barrier method until 7 days after completing a course of antibiotics. 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 be started.

***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 oestrogen or the progestogen or both.

### Effects of COCs on other medicines

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease (e.g. lamotrigine).

Based on *in vitro* inhibition studies and *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrates, an interaction of drospirenone at doses of 3 mg, with the metabolism of other drugs is unlikely.

### Other Interactions

There is a theoretical potential for an increase in serum potassium in women taking BROOKE with other drugs that may increase serum potassium levels. Such drugs include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with oestradiol) with an ACE inhibitor or indomethacin, 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*

### Pregnancy

#### Category B3

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- to 13-fold that anticipated clinically (based on AUC). Virilisation of female foetuses was seen following systemic drospirenone exposure of approximately 2-to 5-fold that anticipated clinically (based on AUC). This effect has previously been described for oestrogens 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 used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. Drosperinone 3 mg + ethinylestradiol 20 micrograms should not be used during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of drosperinone 3 mg + ethinylestradiol 20 micrograms, the preparation must be discontinued immediately. See also CONTRAINDICATIONS.

### Breast-feeding

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

## *4.7 Effects on ability to drive and use machines*

No studies on the effects on the ability to drive and use machines have been performed. No effects on the ability to drive and use machines have been observed in users of COCs.

## *4.8 Undesirable effects*

The most commonly reported adverse reactions with drospirenone/ethinylestradiol when used as oral contraceptive or when used in the treatment of moderate acne vulgaris in women electing to use oral contraception are nausea, breast pain, unscheduled uterine bleeding and genital tract bleeding not further specified. They occur in ≥ 3% of users. The most commonly reported adverse reactions with drospirenone/ethinylestradiol when used for the treatment of PMDD in women electing to use oral contraception are nausea, breast pain and unscheduled uterine bleeding. They occur in > 10% of users.

Serious adverse reactions are arterial and venous thromboembolism.

#### Tabulated list of adverse reactions

The frequencies of adverse drug reactions (ADRs) reported in clinical trials with drospirenone/ethinylestradiol as oral contraceptives and in the treatment of moderate acne vulgaris in women who elect to use oral contraception (n = 3565), as well as drospirenone/ethinylestradiol in the treatment of symptoms of PMDD in women who elect to use oral contraception (n = 289) are summarised in the table below. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. Frequencies are defined as common (≥ 1/100 to < 1/10), uncommon ((≥ 1/1000 to < 1/100) and rare (≥ 1/10000 to < 1/1000). Additional ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under ‘not known’.

| System Organ Class | Common | Uncommon | Rare | Not known |
|---|---|---|---|---|
| **Psychiatric disorders** | Emotional lability, depression / drepressive mood | Decrease and loss of libido [b] | | |
| **Nervous system disorders** | Migraine | | | |

| | | | | |
|---|---|---|---|---|
| **Vascular disorders** | | | **Venous and arterial thromboembolic events *** | |
| **Gastrointestinal disorders** | Nausea [a] | | | |
| **Skin and subcutaneous tissue disorders** | | | | Erythema multiforme |
| **Reproductive system and breast disorders** | Breast pain [a], Unscheduled uterine bleeding [a], Genital tract bleeding not further specified | | | |

Adverse events in clinical studies were coded using the MedDRA dictionary. Different MedDRA terms representing the same medical phenomenon have been grouped together as single adverse reactions to avoid diluting or obscuring the true effect.

* 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

a Incidence in trials evaluating PMDD was Very Common ≥ 1/10
b Incidence in trials evaluating PMDD was Common ≥ 1/100

For venous and arterial thromboembolic events and migraine see also section 4.3 and 4.4.

## Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of COCs are listed below (see also section 4.3 and 4.4):

### *Tumours*

- The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumours (benign and malignant)

### *Other conditions*

- Erythema nodosum
- Women with hypertriglyceridaemia (increased risk of pancreatitis when using COCs)
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema
- Liver function disturbances

- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis
- Chloasma
- Hypersensitivity (including symptoms such as rash, urticaria)

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactionshttps://pophealth.my.site.com/carmreportnz/s/.

## *4.9 Overdose*

There has not yet been any clinical experience of overdose with BROOKE . On the basis of general experience with COCs, symptoms that may occur in case of overdose of active tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)..

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

### Pharmacodynamic properties

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 PRECAUTIONS, ADVERSE 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 oestrogen-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 BROOKE remains to be confirmed.

### Clinical efficacy and safety

#### *Contraception*

In a large multi-centre open trial contraceptive efficacy of drosperinone 3 mg + ethinylestradiol 20 micrograms was evaluated in 1027 women over 13 cycles. The age range was 17 to 36 years. Women with a BMI greater than 35 were excluded from the trial. The primary efficacy variable was the number of unintended pregnancies (Pearl Index) and was 1.29 with an upper two-sided 95% confidence interval of 2.30. When corrected to exclude patient failure the Pearl Index was 0.72 with an upper two-sided 95% confidence interval of 1.69.

A second multi-centre open randomised study to investigate the bleeding pattern, cycle control, contraceptive reliability and general safety of drosperinone 3 mg + ethinylestradiol 20 micrograms in 229 women compared to ethinylestradiol 0.02 mg + desogestrel 0.15 mg in 220 women taken for 21 days followed by pill-free intervals of 7 days over 7 cycles. There were no pregnancies in the drosperinone 3 mg + ethinylestradiol 20 micrograms group 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 third study evaluated lipid and haemostatic and carbohydrate parameters in 29 women taking drosperinone 3 mg + ethinylestradiol 20 micrograms compared to ethinylestradiol 0.02 mg + desogestrel 0.15 mg in 30 women taken for 21 days followed by pill-free intervals 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 3 studies was 1.12 with an upper two-sided 95% confidence interval of 2.01. When corrected to exclude patient failure the Pearl Index was 0.64 with an upper two-sided 95% confidence interval of 1.48.

The parameters of bleeding pattern and cycle control demonstrated a well-controlled and regular bleeding sequence for drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms treated women was equivalent to the comparator group.

***Acne***

Drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 the Table below:

| | **D+EE@ (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 |
| **IGSA Success (Percent of Subjects** | 18.6 | 6.8 | Odds Ratio 3.413 | < 0.0001 |
| **rated "Clear" or "Almost Clear")** | | | (2.146, 5.426 95% C.I.) | |

@ D+EE = drosperinone 3 mg + ethinylestradiol 20 micrograms

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 drosperinone 3 mg + ethinylestradiol 20 micrograms (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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms 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 drosperinone 3 mg + ethinylestradiol 20 micrograms, 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 drosperinone 3 mg + ethinylestradiol 20 micrograms (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 the table below.

| | D+EE@ | | 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 | (0.0137)[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 (1st 14 items) [9] | 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 |

@ D+EE = drosperinone 3 mg + ethinylestradiol 20 micrograms

**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*

### Drospirenoe

#### *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 about 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-sulphate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised 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.*

***Elimination***

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 about 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 CLcr, 50 - 80 mL/min) were comparable to those of women with normal renal function (CLcr, > 80 mL/min). The serum drospirenone levels were on average 37% higher in women with moderate renal impairment (CLcr, 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 volunteers with moderate hepatic impairment was 1.8 times greater than for 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 hyperkalaemia) 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).

**Ethnic groups**

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.

### Ethinylestradiol

***Absorption***

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 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 about 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 sulphate. The metabolic clearance rate of ethinylestradiol is about 5 mL/min/kg.

***Elimination***

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.

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# 6. Pharmaceutical Particulars

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## *6.1 List of excipients*

BROOKE active tablet also contains:

- lactose monohydrate
- maize starch
- crospovidone
- povidone
- 
- magnesium stearate
- iron oxide red

BROOKE non-hormonal tablet also contains:

- lactose monohydrate
- polacrillin potassium
- magnesium sterate

All BROOKE tablets are gluten free.

## *6.2 Incompatibilities*

Not applicable

### *6.3 Shelf life*

2 years.

### *6.4 Special precautions for storage*

Store at or below 25°C.

### *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.

Not all pack sizes may be marketed.

### *6.6 Special precautions for disposal*

Not applicable

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

Zaida is supplied in Australia by:
Maple Healthcare Pty Ltd
Level 8,555 Bourke Street
Melbourne VIC 3000 Australia
info@maplehealthcare.com.au

Zaida is supplied in New Zealand by:
Maple Healthcare Ltd.
TMF Group, Level 11,
41 Shortland Street,
Auckland, 1010, New Zealand
info@maplehealthcare.com.au

## 9. Date of First Approval

11 June 2015

## 10. Date of Revision of the Text

27 March 2026

**Summary table of changes**

| Section | Summary of new information |
|---|---|
| | Revise to SPC format |
| Throughout | Brand name change from ZAIDA to BROOKE |
| 3 | Include bioconvex |
| 6.1 | Updated excipients |
| 6.5 | Updated nature and contents of container details |
| 8 | Updated Sponsor details |
| 4.8 | Update ADR website |
| 4.9 | Update overdose statement |