# NEW ZEALAND DATA SHEET

# BROOKLNN

## 1. Product Name

BROOKLYNN, drospirenone 3 mg and ethinylestradiol 30 micrograms, tablet.

## 2. Qualitative and Quantitative Composition

Each blister strip holds 21 active hormonal tablets and 7 non-hormonal tablets. Each active hormonal tablet contains 3 mg drospirenone and 30 micrograms of ethinylestradiol.

Excipient(s) with known effect

BROOKLYNN contains lactose.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical Form

Active hormonal tablets: round, light brown, uncoated biconvex tablets debossed with ‘156’ 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*

Oral contraception

### *4.2 Dose and method of administration*

BROOKLYNN is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection.

**How to take BROOKLYNN**

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 and may not have finished before the start of the next pack.

**How to start BROOKLYNN**

START WITH THE FIRST TABLET FROM THE GREEN SECTION MARKED WITH THAT DAY OF THE WEEK, in accordance with one of the following:

- 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 brown 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 if this occurs a barrier contraceptive method is recommended in addition for the first 7 days of tablet taking.

- Changing from another combined oral contraceptive (COC) vaginal ring, or transdermal patch

The woman should start with BROOKLYNN preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case vaginal ring or transdermal patch has been used, the woman should start using BROOKLYNN preferably on the day of removal of the ring or patch, but at the latest 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 IUS on the day of its removal, or from an injectable when the next injection would be due), but should in all of these cases, the woman should be advised to additionally use a barrier contraceptive 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.

For breastfeeding women see section 4.6.

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later than this, the woman should be advised to additionally use a barrier contraceptive method for the first 7 days of tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before starting BROOKLYNN or the woman has to wait for her first menstrual period.

## 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 (rows 1 - 3 of the blister):

If the woman is **less than 12 hours** late in taking any 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 12 hours** late in taking any active tablet, contraceptive protection may be reduced.

There is a particularly high risk of pregnancy if tablets are missed at the beginning or end of the pack. If tablets are missed in the first week of taking active tablets and intercourse took place in the preceding 7 days, the possibility of pregnancy should be considered. The management of missed tablets can be guided by the following two basic rules:

1. Active (hormonal) tablet-taking must never be discontinued for longer than 7 days

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

Accordingly the following advice can be given in daily practice:

**Week 1**

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 pregnancy should be considered. The more tablets are missed and the closer they are to the placebo tablet phase the higher the risk of pregnancy.

**Week 2**

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 precautions for 7 days.

**Week 3**

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 would be 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 7 tablets from the last row (placebo) 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 for up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

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

## 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, 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.

## How to shift periods or how to delay a period

To delay a period the woman should continue with active tablets from another calendar pack of BROOKLYNN without taking the placebo tablets from her current calendar pack. The extension can be carried on for as long as desired until the end of the second calendar pack. During the extension

the woman may experience breakthrough bleeding or spotting. Regular intake of BROOKLYNN is then resumed with the next pack.

## *4.3 Contraindications*

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

- Thrombosis (venous or arterial) present or in history (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident)
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- Presence or history of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Disturbed lipometabolism
- 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 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
- Presence or history of liver tumours (benign or malignant)
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the components of BROOKLYNN

## *4.4 Special warnings and precautions for use*

The clinical and epidemiological evidence for oestrogen/progestogen combinations like BROOKLYNN is predominantly based on experience with COCs in general. Therefore, the following warnings related to the use of COCs apply also to the use of BROOKLYNN.

If any of the conditions/risk factors mentioned below is 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 COC use should be discontinued.

### Circulatory disorders

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

Venous thromboembolism (VTE) manifesting as DVT and/or PE may occur during the use of all COCs. The risk of 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 first study mentioned:

**Incidences[+] (with 95% Confidence Interval) of thromboembolic events [#]**

| Type of Event | D+E[♦] (28,621 WY) | | LNG-containing (31,415WY) | | Other OC's (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 |

♦ Drosperinone 3 mg + ethinylestradiol 30 micrograms (D+E)

+ 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 users of drosperinone 3 mg + ethinylestradiol 30 micrograms 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 drosperinone 3 mg + ethinylestradiol 30 micrograms cases was very small (1.2% of all cases making the risk estimates unreliable). The relative risk for drosperinone 3 mg + ethinylestradiol 30 micrograms 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 drosperinone 3 mg + ethinylestradiol 30 micrograms 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 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 thromboembolism (venous and/or arterial) 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/$m^2$)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation, 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.

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 headaches during COC use in particular the onset of migraine (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, hyperhomocysteinemia, 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 (< 0.05 mg ethinylestradiol).

## Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus (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 an 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, 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 using COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. The anti-mineralocorticoid effect of drospirenone may counteract ethinylestradiol-induced increases in blood pressure observed in normotensive women using other COCs. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC, 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 or kidney function may necessitate the discontinuation of COC use until markers of liver or kidney 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 (containing 50 micrograms ethinylestradiol) COCs. 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 brown active tablet contains 72.01 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 BROOKLYNN, guided by the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections. This should be repeated at least annually during the use of BROOKLYNN. 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 BROOKLYNN. 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 preparations like BROOKLYNN 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 BROOKLYNN may be reduced in the event of missed light brown active tablets, gastrointestinal disturbances (e.g. vomiting, diarrhoea) during active tablet-taking or concomitant medication (see section 4.2 and 4.5).

## Reduced cycle control

With oestrogen/progestogen combinations, 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 while taking the 7 placebo tablets. 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.

### Paediatric use

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

### Use in the elderly

BROOKLYNN is not indicated after menopause.

### Patients with hepatic impairment

BROOKLYNN is contraindicated in women with severe hepatic diseases (see section 4.3).

### Patients with renal impairment

BROOKLYNN is contraindicated in women with severe renal insufficiency or acute renal failure (see section 4.3).

### Laboratory tests

The use of preparations like BROOKLYNN 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 BROOKLYNN

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 started.

Women on long-term treatment with hepatic-enzyme inducing drugs, experts have recommended to increase the contraceptive steroid doses. If a high contraceptive dosage is most desirable or appears to be unsatisfactory or unreliable, e.g. in the case of irregular bleeding, another method of contraception should be advised.

***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.

### Influence of COCs on other medicines

Oral contraceptives may interfere with the metabolism of other medicines. 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, drospirenone at doses of 3 mg shows little propensity to interact with the metabolism of other medicines.

### Other interactions

There is theoretical potential for an increase in serum potassium in women taking BROOKLYNN with other medicines that may increase serum potassium levels. Such medicines include: angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in a study evaluating the interaction of drospirenone (combined with oestradiol) with an ACE inhibitor no clinically or statistically significant differences in serum potassium concentrations in mildly hypertensive postmenopausal women maintained on enalapril therapy were observed in comparison with placebo.

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

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

The administration of BROOKLYNN is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. If pregnancy occurs during treatment with BROOKLYNN the preparation must be discontinued immediately.

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 rabbits or rats.

Dose-dependent feminisation of male foetuses and virilisation of female foetuses were seen following administration of a combination of predrospirenone 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 - 5 fold than 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. See also section 4.3.

The available data regarding the use of drosperinone 3 mg + ethinylestradiol 30 micrograms during pregnancy is too limited to permit conclusions concerning negative effects of BROOKLYNN on pregnancy, health of the foetus or neonate.

### 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 in 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 are nausea and breast pain. They occur in > 6% of users.

Serious adverse reactions are arterial and venous thromboembolism.

The most commonly reported adverse reactions with drospirenone/ethinylestradiol (N=4897) 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). Serious adverse reactions are arterial and venous thromboembolism. Additional ADRs identified only during post marketing 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 / depressive mood Decrease and loss of libido | | | |
| **Nervous system disorders** | Migraine | | | |
| **Vascular disorders** | | | Venous and arterial thromboembolic events* | |
| **Gastrointestinal disorders** | Nausea | | | |
| **Skin and subcutaneous tissue disorders** | | | | Erythema multiforme |
| **Reproductive system and breast disorders** | Breast pain, Unscheduled uterine bleeding, 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

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 reactions https://pophealth.my.site.com/carmreportnz/s/.

## *4.9 Overdose*

There has not yet been any clinical experience of overdose with BROOKLYNN. There have been no reports of serious deleterious effects from overdose in preclinical studies. On the basis of general experience with COCs, symptoms that may occur in case of taking an overdose 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 effects

BROOKLYNN is a combined oral contraceptive (COC) tablet containing the synthetic progestogen, drospirenone, and the synthetic oestrogen, ethinylestradiol. The contraceptive effect of BROOKLYNN is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in cervical secretion. When BROOKLYNN is taken according to instructions, the egg cells are prevented from maturing to the point at which they can be fertilised, the cervical mucus remains thick so as to constitute a barrier to sperm, and the endometrium is rendered unreceptive to implantation.

As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties, 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. In addition, with the higher dosed COCs (50 micrograms ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breast, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.

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 and 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, oestrogenic, 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.

### Clinical efficacy and safety

2,274 women have received drosperinone 3 mg + ethinylestradiol 30 micrograms in clinical studies over study periods between 6 and 26 cycles, giving a total of 30,110 cycles. The assessment of the contraceptive efficacy was based on seven phase II and phase III studies. These studies comprised 2,263 valid cases for the efficacy evaluation and 29,735 cycles. Five of these studies were comparative studies. The observation periods were between 6 and 26 cycles. For the calculation of the Pearl Index, all cycles in which at least 19 tablets were taken were counted, as were all pregnancies under treatment. This gives a slight over-estimation of the true Pearl Index. For the corrected Pearl Index calculation cycles in which condom use was documented were excluded.

The uncorrected Pearl Index was 0.57. The corrected Pearl Index, discounting pregnancies due to documented user failure was 0.09. In comparative studies the Pearl Index for desogestrel 150 mg and ethinylestradiol 30 micrograms was 0.43 and 0.09 respectively. The results for both preparations were comparable to the range known for other low dosed oral contraceptives containing 30 micrograms ethinylestradiol.

For drosperinone 3 mg + ethinylestradiol 30 micrograms treated women the probability of becoming pregnant for the time of continuous use was estimated. After two years of drosperinone 3 mg + ethinylestradiol 30 micrograms use, the estimated failure rate was still below 0.01.

Cycle control was evaluated on the basis of 2 extended phase III studies in 1,313 women taking drosperinone 3 mg + ethinylestradiol 30 micrograms. The total number of cycles valid for analysis was 20,787. Between 40 - 60% of women reported intermenstrual bleeding, however the number of cycles with bleeding was only 7.5 - 9%. Between 75 -80% of women had no irregular bleeding in the first cycle. This increased 85 - 90% in the next 2 cycles. A constant low frequency of less than 10% was observed through the end of both studies (13 and 26 cycles). Spotting occurred in 6 - 7% of all

cycles and heavy/normal breakthrough bleedings in less than 0.5% of cycles. Spotting and breakthrough bleeding combined occurred in less than 2% of all cycles. The incidence of amenorrhoea was less than 1 % and 1.6% in the two studies.

Drosperinone 3 mg + ethinylestradiol 30 micrograms produced a decrease in the duration and intensity of the withdrawal bleed. Drosperinone 3 mg + ethinylestradiol 30 micrograms had no adverse effect on blood pressure or body weight.

## *5.2 Pharmacokinetic properties*

### Drospirenone

#### *Absorption*

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum serum concentrations of about 37 ng/mL are reached at about 1 - 2 hours after single ingestion. Absolute bioavailability is between 76 and 85%. Concomitant ingestion of food has no influence on bioavailability.

#### *Distribution*

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of 1.6 ± 0.7 hours and 27.0 ± 7.5 hours, 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, 95 - 97% are non-specifically bound to albumin. The ethinylestradiol induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is about 3.7 - 4.2 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 to a minor extent by cytochrome P450 3A4 based on *in vitro* data. When drospirenone was acutely co-administered with ethinylestradiol, no direct interaction was found.

#### *Elimination*

The metabolic clearance rate from serum is about 1.2 - 1.5 mL/min/kg. Drospirenone is not excreted 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 hours.

#### *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 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 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 Cmax values. The mean terminal half-life of drospirenone for volunteers with moderate hepatic impairment was 1.8 times than for volunteers with normal hepatic function. An 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, two 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. Based on the results of this study it can be concluded that drospirenone/ethinylestradiol 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 54 - 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 while no change was observed in the others.

***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%), and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2.8 - 8.6 L/kg was determined.

***Metabolism***

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. It 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 2.3 - 7 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 1.4 - 2.1.

## *5.3 Preclinical safety data*

Animal toxicity studies for human risk estimation were performed for both components of the preparation, ethinylestradiol and drospirenone, and in certain cases with the combination.

No effects which might indicate an unexpected risk to humans were observed during systemic tolerance studies after repeated administration.

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it should be borne in mind that sex steroids might stimulate the growth of hormone-dependent tissues and tumours.

Studies on embryotoxicity and teratogenicity and the evaluation of effects of the combination on the fertility of parent animals, foetal development, lactation and reproductive performance of the offspring gave no indication of a risk of adverse effects in humans after recommended use of the preparation. Especially, the feminising effect in male rat foetuses after treatment of pregnant animals during the sensitive phase of foetal sex differentiation does not raise concerns with regard to human safety assessment since it occurred only after drug exposures which are substantially higher than those observed in users of BROOKLYNN.

Although interactions between drospirenone and DNA of liver cells which indicate a genotoxic potential were found in in vitro and in vivo studies on rats, no such finding was observed in human liver cells in vitro. Furthermore, mutagenicity tests gave no indication of a mutagenic potential of the compound. Thus current knowledge indicates no relevant mutagenic potential.

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

BROOKLYNN active tablet also contains:

- lactose monohydrate
- maize starch
- crospovidone
- povidone
- magnesium stearate
- sunset yellow (E110)
- indigo carmine (E132)

BROOKLYNN non-hormonal tablet also contains:

- lactose monohydrate
- polacrillin potassium
- magnesium sterate

All BROOKLYNN 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*

BROOKLYNN tablets are contained in PVDC/PVC/Aluminium foil blister packs. The blister strips are contained within a tri-laminated foil pouch. Each blister contains 21 round light brown tablets followed by 7 round white placebo tablets.

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

Not all pack sizes may be marketed.

### *6.6 Special precautions for disposal*

Not applicable.

## 7. Medicines Schedule

Prescription Medicine

## 8. Sponsor Details

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

BROOKLYNN 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 |
|---|---|
| All | Revise to SPC format |
| Throughout | Brand name change from ZAIDA to BROOKLYNN and spelling error corrections |
| 6.5 | Details of container and contents revised |
| 8 | Sponsor details updated |
| 4.8 | Updated ADR website |
| 4.9 | Updated overdose statement |