

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## AUSTRALIAN PRODUCT INFORMATION

### NEXTSTELLIS™ (ESTETROL (AS MONOHYDRATE) AND DROSPIRENONE) TABLETS

#### 1. NAME OF THE MEDICINE

Estetrol (as monohydrate) and drospirenone

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Estetrol (E4) is a synthetic analogue of a native human estrogen and drospirenone is a synthetic progestational compound.

Each active tablet contains 14.2 mg estetrol (equivalent to 15 mg of estetrol monohydrate) and 3 mg of drospirenone.

Excipients with known effect: lactose.

For the full list of excipients, see *section 6.1 List of Excipients*.

#### 3. PHARMACEUTICAL FORM

Film-coated tablets.

Active tablet: Pink tablet embossed with a drop-shaped logo on one side.

Inactive tablet: White tablet embossed with a drop-shaped logo on one side.

#### 4. CLINICAL PARTICULARS

##### 4.1. Therapeutic Indications

NEXTSTELLIS is indicated for use by women of reproductive potential to prevent pregnancy.

## 4.2. Dose and Method of Administration

### Dosage

NEXTSTELLIS is dispensed in a blister pack. NEXTSTELLIS should be started using instructions for starting or switching in Table 1.

**Table 1: Instructions for starting or switching NEXTSTELLIS**

<p><b>Starting NEXTSTELLIS in women with no current use of hormonal contraception</b></p>	<p><b>Important:</b></p> <ul style="list-style-type: none"> <li>• Consider the possibility of pregnancy prior to initiation of this product.</li> <li>• Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e. the first day of her menstrual bleeding). If not starting on the first day of menses for any reason, use a non-hormonal contraceptive (condom and spermicide) as back-up until tablets have been taken for 7 days in a row.</li> </ul> <ol style="list-style-type: none"> <li>1. Take the first tablet from the purple area on the blister pack corresponding to the day of the week.</li> <li>2. Follow the direction of the arrows on the blister pack until all the tablets have been taken.</li> <li>3. A period should begin 2-3 days after starting to take the white inactive tablets and may not have finished before recommencing active tablets.</li> <li>4. Always start a new blister pack on the same day of the week as the previous blister pack.</li> </ol>
<p><b>Switching from another contraceptive method to NEXTSTELLIS</b></p>	<p><b>Start NEXTSTELLIS:</b></p>
<ul style="list-style-type: none"> <li>• Combined Oral Contraceptive (COC)</li> </ul>	<ul style="list-style-type: none"> <li>• On the day after the last active tablet (the last tablet containing the active substances) of her previous COC.</li> </ul>
<ul style="list-style-type: none"> <li>• Transdermal patch</li> </ul>	<ul style="list-style-type: none"> <li>• On the day when the next application would have been scheduled.</li> </ul>
<ul style="list-style-type: none"> <li>• Vaginal ring</li> </ul>	<ul style="list-style-type: none"> <li>• On the day of removal.</li> </ul>
<ul style="list-style-type: none"> <li>• Injection</li> </ul>	<ul style="list-style-type: none"> <li>• On the day when the next injection would have been scheduled.</li> </ul>
<ul style="list-style-type: none"> <li>• Hormone-medicated intrauterine contraceptive</li> </ul>	<ul style="list-style-type: none"> <li>• On the day of removal.</li> </ul>
<ul style="list-style-type: none"> <li>• Implant</li> </ul>	<ul style="list-style-type: none"> <li>• On the day of removal.</li> </ul>
<ul style="list-style-type: none"> <li>• Progestin-only tablet</li> </ul>	<ul style="list-style-type: none"> <li>• On the day after the last tablet was taken.</li> </ul>

**Refer to the Consumer Medicine Information for additional instructions for counselling patients concerning proper use**

### Starting NEXTSTELLIS After Abortion or Miscarriage

#### *First-Trimester*

- After a first-trimester abortion or miscarriage, NEXTSTELLIS may be started immediately. An additional method of contraception is not needed if NEXTSTELLIS is started within 5 days after termination of the pregnancy.
- If NEXTSTELLIS is not started within 5 days after termination of the pregnancy, the woman should use additional non-hormonal contraception (such as condoms and spermicide) until pink tablets have been taken for 7 days in a row.

#### *Second-Trimester*

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start contraceptive therapy with NEXTSTELLIS after having ruled out pregnancy. Use of a non-hormonal contraceptive (such as condom and spermicide) is recommended until pink tablets have been taken for 7 days in a row.

See *section 4.3 Contraindications* and *section 4.4 Special Warnings and Precautions for Use*.

### Starting NEXTSTELLIS After Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with NEXTSTELLIS after having ruled out pregnancy. Use of a non-hormonal contraceptive (such as condom and spermicide) is recommended until pink tablets have been taken for 7 days in a row.

If the woman is breastfeeding the use of a non-hormonal method of contraception is to be recommended until the woman discontinues breast feeding (see *section 4.6 Fertility, Pregnancy and Lactation*).

See *section 4.3 Contraindications*, *section 4.4 Special Warnings and Precautions for Use* and *section 4.6 Fertility, Pregnancy and Lactation*.

### **Method of Administration**

NEXTSTELLIS (pink active and white inactive tablets) is swallowed whole once a day. Take one tablet daily for 28 consecutive days. Once established on NEXTSTELLIS the administration cycle will involve 24 active pink tablets taken consecutively followed by 4 inactive white tablets. This may be across different blister packs. Tablets must be taken every day at about the same time of the day so that the interval between consecutive tablets is the same.

Missed Doses

**Table 2: Instructions for missed NEXTSTELLIS**

<ul style="list-style-type: none"> <li>• If one pink active tablet is missed</li> </ul>	Take the missed tablet as soon as possible. Continue taking one tablet a day until the blister pack is finished.
<ul style="list-style-type: none"> <li>• If two pink active tablets are missed in week 1 or week 2</li> </ul>	Take the two missed tablets as soon as possible and the next two tablets the next day. Continue one tablet a day until the blister pack is finished. If the woman has sex within 7 days after missing tablets, non-hormonal contraception (such as condoms and spermicide) should be used until pink tablets have been taken for 7 days in a row.
<ul style="list-style-type: none"> <li>• If two pink active tablets are missed in week 3, or three or more pink active tablets are missed in a row in weeks 1, 2 or 3</li> </ul>	Start a new blister pack that same day. <i>See section 6.6 Special Precautions for Disposal</i> for instructions on how to dispose of the unused blister pack. If the woman has sex within 7 days after missing tablets, non-hormonal contraception (such as condoms and spermicide) should be used as back-up until pink tablets have been taken for 7 days in a row.
<ul style="list-style-type: none"> <li>• If one or more white inactive tablets are missed</li> </ul>	Skip the missed tablet days and continue taking one tablet a day until the blister pack is finished.

In Case of Gastrointestinal Disturbances

If vomiting or diarrhea occurs within 3-4 hours after tablet-taking, the new tablet (scheduled for the next day) should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than two tablets are missed, the advice concerning missed tablets, including using non-hormonal contraception given above is applicable.

**4.3. Contraindications**

COCs, including NEXTSTELLIS, 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 risk of venous thromboembolism (VTE) (*see section 4.4 Special Warnings and Precautions for Use*)
  - Current VTE (on anticoagulants) or history of deep venous thrombosis (DVT) or pulmonary embolism (PE)
  - Known hereditary or acquired predisposition for VTE, such as APC-resistance (including factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
  - Major surgery with prolonged immobilisation
  - A high risk of VTE due to the presence of multiple risk factors

- Presence or risk of arterial thromboembolism (ATE) (see *section 4.4 Special Warnings and Precautions for Use*)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
  - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin antibodies and lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - A high risk of ATE due to the presence of multiple combined risk factors such as: heavy cigarette smoking (around 15 or more per day); positive family history (ATE in a sibling or parent especially at relatively early age, e.g., below 50); and over 35 years of age
  - A high risk of ATE due to the presence of one serious risk factor such as:
    - § diabetes mellitus with vascular symptoms
    - § severe hypertension
    - § severe dyslipoproteinaemia
- Pancreatitis, or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease 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)
- Adrenal insufficiency
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to any of the ingredients contained in NEXTSTELLIS

#### **4.4. Special Warnings and Precautions for Use**

##### **Identified Precautions**

##### Thromboembolic Disorders and Other Vascular Problems

- Stop NEXTSTELLIS if an arterial or venous thrombotic/thromboembolic event occurs.

- Stop NEXTSTELLIS if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue NEXTSTELLIS during prolonged immobilisation. If feasible, stop NEXTSTELLIS at least four weeks before and through two weeks after major surgery, or other surgeries known to have an elevated risk of thromboembolism.
- Start NEXTSTELLIS no earlier than four weeks after delivery in women who are not breast feeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.
- Before starting NEXTSTELLIS, evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. NEXTSTELLIS is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases (see *section 4.3 Contraindications*).

#### Arterial Events

COCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and females with hypertension, dyslipidaemia, diabetes, or obesity. Cigarette smoking increases the risk of serious cardiovascular events from COC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

#### *Symptoms of ATE*

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a COC.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a TIA.

Symptoms of myocardial infarction can include:

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

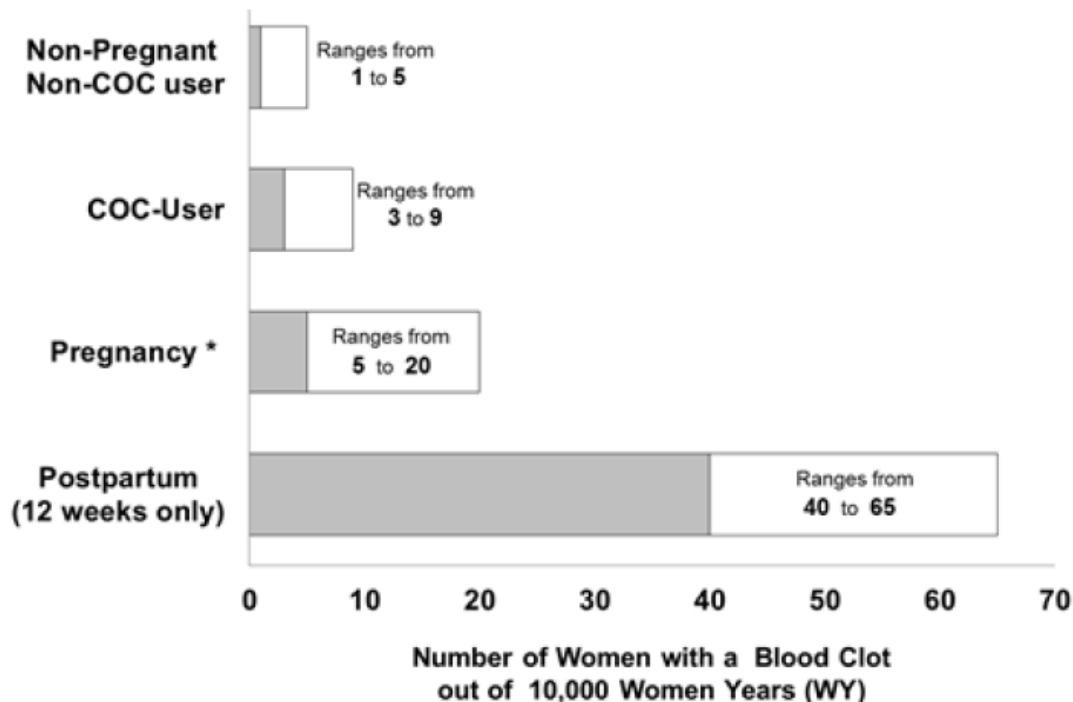
### Venous Events

Use of COCs increases the risk of venous thromboembolic events, such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs (see *section 4.3 Contraindications*). While the increased risk of VTE associated with use of COCs is well established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The rate of VTE in females using COCs has been estimated to be 3 to 9 cases per 10,000 woman-years for COCs.

The risk of VTE is highest during the first year of use of a COC and when restarting hormonal contraception after a break of four weeks or longer. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.

Figure 1 shows the risk of developing a VTE for women who are not pregnant and do not use COCs, for women who use COCs, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: if 10,000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

**Figure 1: Likelihood of Developing a VTE**



\* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

Products that contain low-dose ethinylestradiol (<50 microgram ethinylestradiol) combined with levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Based on clinical trial incidence and haemostatic profile, the risk of VTE with NEXTSTELLIS is considered to be not higher than levonorgestrel-containing COCs. The VTE risk is highest in the first ever year of COC use. There is also some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

Epidemiologic studies of NEXTSTELLIS evaluating the risk of VTE in females of reproductive potential to prevent pregnancy have not been performed. In two large prospective studies (n = 3,632), one in Europe/Russia (NCT02817828; C301) and one in North America (NCT02817841; C302) on the use of NEXTSTELLIS for the prevention of pregnancy in women 16-50 years of age, there was one reported VTE in the Europe/Russia study, giving an annual incidence rate of 3.66 per 10,000 women/year. In a Phase 2 study comparing NEXTSTELLIS (n = 38) to a COC containing ethinylestradiol 30 µg/levonorgestrel 150 µg (n = 29) and ethinylestradiol 20 µg/drospirenone 3 mg (n = 31) over 6 cycles, NEXTSTELLIS did not result in significant changes from baseline in any of the tested haemostatic parameters. NEXTSTELLIS was associated with smaller percentage change from baseline compared to ethinylestradiol/levonorgestrel for the pro-coagulation factors ETP-based activated protein C resistance (30% vs 164%) and prothrombin fragments 1+2 (23% vs 71%) whereas both NEXTSTELLIS and



ethinylestradiol/levonorgestrel had limited effect on Factor VII (-3% vs -5%), factor VIII (5% vs 3%), prothrombin (7% vs 13%) and APTT-based activated protein C resistance (0% vs 5%). The anti-coagulation factors were minimally affected by both NEXTSTELLIS and ethinylestradiol/levonorgestrel: antithrombin (1% vs -5%), protein S (-4% vs -5%), free protein S (5% vs -3%) and protein C (2% vs 7%). The fibrinolytic parameters D-dimer was minimally changed from baseline with NEXTSTELLIS (4%) vs ethinylestradiol/levonorgestrel (7%). Ethinylestradiol/drospirenone had an overall greater impact on haemostasis markers than NEXTSTELLIS and ethinylestradiol/levonorgestrel.

#### *Symptoms of VTE (DVT and PE)*

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a COC.

#### *Symptoms of DVT can include*

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

#### *Symptoms of PE can include*

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

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

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

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

**A checklist for prescribers is available on [nextstellis.com.au](http://nextstellis.com.au).** The checklist for prescribers is intended to provide information concerning the risk of thromboembolism in association with certain COCs.

### Hyperkalaemia

Drospirenone is devoid of any androgenic, estrogenic, glucocorticoid and antiglucocorticoid activity. This, in combination with the anti-mineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone.

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 (see *section 4.5 Interactions with Other Medicines and Other Forms of Interactions*).

In the clinical development studies with NEXTSTELLIS no trend in serum potassium levels was noted. Most women with hyperkalaemia in the clinical development studies of NEXTSTELLIS had only mild potassium elevations and/or isolated increases that returned to normal while still on study medication. In two pivotal trials (n = 3,632) for the prevention of pregnancy in women 16-50 years of age, no adverse reactions were attributed to hyperkalaemia and no subject discontinued due to elevated potassium levels.

### Hypertension

NEXTSTELLIS is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease (see *section 4.3 Contraindications*). For all women, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop NEXTSTELLIS if blood pressure rises significantly.

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 any oestrogen-induced increases in blood pressure. In the two large prospective clinical trials with NEXTSTELLIS (n = 3,632) no meaningful mean changes in blood pressure or heart rate were observed.

### Age-Related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a COC for women over 35 years, such as:

- Hypertension
- Diabetes
- Dyslipidaemia
- Obesity

## Adverse Carbohydrate and Lipid Metabolic Effects

### *Hyperglycaemia*

NEXTSTELLIS is contraindicated in women who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease (see *section 4.3 Contraindications*). NEXTSTELLIS may decrease glucose tolerance. Carefully monitor prediabetic and diabetic women who are using NEXTSTELLIS.

In a 6-month Phase 2 clinical trial NEXTSTELLIS did not induce a change in glucose or insulin response upon oral glucose dosing, and fasting levels of HbA1c and glucose were unchanged. Slightly increased fasting levels of insulin and C-peptide were observed with NEXTSTELLIS at Cycle 6, but less than noted with ethinylestradiol 30 µg/levonorgestrel 150 µg and ethinylestradiol 20 µg/drospirenone 3 mg.

### *Dyslipidaemia*

Consider alternative contraception for women with uncontrolled dyslipidaemia. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs. In a Phase 2 study comparing NEXTSTELLIS (n = 34), ethinylestradiol 30 µg/levonorgestrel 150 µg (n = 27) and ethinylestradiol 20 µg/drospirenone 3 mg (n = 30), NEXTSTELLIS demonstrated a neutral effect on lipid parameters.

**Table 3: Percentages change from baseline in lipids and lipoproteins. median [min, max] (PP population)**

Parameter	NEXTSTELLIS 15 mg/3 mg	EE/LNG 30 µg/150 µg	EE/DRSP 20 µg/3 mg
	n = 34	n = 27	n = 30
Cholesterol (mg/dL)	4.0 [-20.0, 27.0]	1.0 [-16.0, 25.0]	6.5 [-20.0, 39.0] *
HDL Cholesterol (mg/dL)	4.0 [-24.0, 33.0] <sup>1</sup>	-16.0 [-35.0, 11.0] * <sup>1,3</sup>	8.5 [-17.0, 45.0] * <sup>3</sup>
Apolipoprotein A1 (mg/dL)	5.0 [-20.0, 23.0] * <sup>1,2</sup>	-3.0 [-23.0, 43.0] * <sup>1,3</sup>	19.5 [-5.0, 64.0] * <sup>2,3</sup>
LDL Cholesterol (mg/dL)	-2.0 [-24.0, 32.0]	7.0 [-36.0, 57.0]	-5.0 [-38.0, 58.0]
Apolipoprotein B (mg/dL)	4.0 [-20.0, 48.0] * <sup>1,2</sup>	23.0 [-12.0, 70.0] * <sup>1,3</sup>	11.5 [-17.0, 61.0] * <sup>2,3</sup>
HDL Cholesterol/LDL Cholesterol	0.0 [-25.0, 80.0] <sup>1</sup>	-17.0 [-53.0, 40.0] * <sup>1,3</sup>	17.0 [-46.0, 100.0] * <sup>3</sup>
Triglycerides (mg/dL)	24.0 [-28.0, 159.0] * <sup>2</sup>	28.0 [-17.0, 161.0] * <sup>3</sup>	65.5 [23.0, 198.0] * <sup>3</sup>
Lipoprotein-a (nmol/L)	0.0 [-40.0, 36.0]	0.0 [-55.0, 46.0]	0.0 [-57.0, 32.0]

DRSP = drospirenone; E4 = estetrol; EE = ethinylestradiol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LNG = levonorgestrel; PP = per protocol

\* Statistically significant (p < 0.05) change from baseline;

<sup>1,2,3</sup> Statistically significant ( $p < 0.05$ ) between treatments: 1 = NEXTSTELLIS vs EE/LNG; 2 = NEXTSTELLIS vs EE/DRSP; 3 = EE/LNG vs EE/DRSP

### Bleeding Patterns and Amenorrhea

In two large prospective studies ( $n = 3,632$ ), one in Europe/Russia (C301) and one in North America (C302) on the use of NEXTSTELLIS for the prevention of pregnancy in women 16-50 years of age, the vaginal bleeding experience was recorded every day using a paper diary.

#### *Unscheduled Bleeding and Spotting*

Women using NEXTSTELLIS may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first month of use. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy.

After an initial incidence of 27.1% in Cycle 1 (pooled C301 and C302), the overall incidence of unscheduled bleeding and/or spotting ranged between 15% and 20% per cycle. The majority of bleeding and/or spotting episodes concerned spotting-only, implying that in each cycle, approximately 90% of the subjects did not experience unscheduled bleeding requiring the use of sanitary protection. From Cycles 2 through 12 the mean number of unscheduled bleeding/spotting days ranged between 0.4 and 0.6 days per cycle; the mean number of bleeding days was 0.2 to 0.3. Incidence of unscheduled bleeding and/or spotting was higher when including only cycles with one missed active pill (18.2% to 31.3%) and became more irregular when including only cycles with at least two active missed pills.

#### *Scheduled Bleeding*

Women who use NEXTSTELLIS may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. Based on subject diaries from clinical trials, absence of scheduled bleeding occurred in 9.7% to 11.3% of subjects per cycle, implying that 88.7% to 90.3% of the women did have their scheduled withdrawal bleeding in studies (C301 and C302). There were on average 4.9 to 5.6 scheduled bleeding-spotting days in a cycle, consisting of equal numbers of bleeding and spotting days. The median number of bleeding-spotting days in scheduled episodes was 4.0 to 5.0 days.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

Discontinuation due to bleeding pattern-related events was low from two different large studies (3.4% and 2.6%) (see *section 5.1 Pharmacodynamic Properties – Clinical Trials*).

### COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who take COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. NEXTSTELLIS is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of NEXTSTELLIS, the preparation must be discontinued immediately (see *section 4.3 Contraindications*).

### Depression

Carefully observe women with a history of depression and discontinue NEXTSTELLIS if depression recurs to a serious degree. Data on the association of COCs with onset of depression or exacerbation of existing depression are limited.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

### Carcinoma of the Breast and Cervix

NEXTSTELLIS is contraindicated in women who currently have or have had breast cancer because breast cancer can be hormonally sensitive (see *section 4.3 Contraindications*).

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behaviour and other factors.

### Effect on Binding Globulins

The effect of NEXTSTELLIS (n = 34) was compared to ethinylestradiol 30 µg/levonorgestrel 150 µg (n = 27) and ethinylestradiol 20 µg/drospirenone 3 mg (n = 30) for differences in effects on binding globulins in a Phase 2 study. Sex Hormone Binding Globulin (SHBG) was increased in all three treatment groups and most pronounced in users of ethinylestradiol/drospirenone (+251%). The increases observed in users of NEXTSTELLIS (+55%) and ethinylestradiol/levonorgestrel (+74%) were smaller and comparable. Similarly, levels of Corticosteroid Binding Globulin (CBG) and Thyroxin Binding Globulin were found to increase, especially in the ethinylestradiol-containing COC groups. NEXTSTELLIS slightly increased the levels of cortisol, but less than observed with both comparators. Thyroid hormones were minimally affected.

### Hereditary Angioedema

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

### Chloasma

Chloasma may occur with NEXTSTELLIS use, especially in women with a history of chloasma gravidarum. Advise women with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using NEXTSTELLIS.

### Race/Ethnicity

No clinically significant difference was observed between the pharmacokinetics of E4 or drospirenone depending on race (see *section 5.2 Pharmacokinetic Properties*).

### Body Mass Index (BMI)/Body Weight

The safety and efficacy of NEXTSTELLIS in women with a BMI  $\geq 35$  kg/m<sup>2</sup> have not been evaluated. In Study C302 (see *section 5.1 Pharmacodynamic Properties – Clinical Trials*), 23% of subjects had a BMI between 30 and 35 kg/m<sup>2</sup>. There was no difference in safety or efficacy based on stratification by BMI.

### Other conditions

Worsening of Crohn's disease and ulcerative colitis has been reported by women using COCs.

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.

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.

### **Use in Hepatic Impairment**

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

### Liver Tumours

NEXTSTELLIS is contraindicated in women with benign and malignant liver tumours (see *section 4.3 Contraindications*).

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.

#### Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinylestradiol-containing medications, such as COCs. Women using medications containing estrogens other than ethinylestradiol had a rate of ALT elevation similar to those not receiving any estrogens. NEXTSTELLIS contains estetrol monohydrate rather than ethinylestradiol, but as no data are available for co-administration with this Hepatitis C combination drug regimen, caution is warranted.

#### **Use in Renal Impairment**

NEXTSTELLIS is contraindicated in women with severe renal impairment (see *section 4.3 Contraindications*).

In subjects with creatinine clearance (CrCL) of 50–79 mL/min, serum drospirenone levels were comparable to those in a control group with CrCL  $\geq$  80 mL/min. In subjects with CrCL of 30–49 mL/min, serum drospirenone concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalaemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs (see *section 4.4 Special Warnings and Precautions for Use*, *section 4.5 Interactions with Other Medicines and Other Forms of Interactions* and *section 5.2 Pharmacokinetic Properties*).

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CrCL, 50-80 mL/min) were comparable to those of women with normal renal function (CrCL, > 80 mL/min). The serum drospirenone levels were on average 37% higher in women with moderate renal impairment (CrCL, 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.

#### **Use in the Elderly**

NEXTSTELLIS is not indicated after menopause.

#### **Paediatric Use**

Safety and efficacy of NEXTSTELLIS have been established in women of reproductive potential, 16-50 years of age. NEXTSTELLIS is only indicated after menarche.

## Effects on Laboratory Tests

Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity.

Caution is warranted for co-administration of NEXTSTELLIS with the Hepatitis C combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see *section 4.4 Special Warnings and Precautions for Use*).

## 4.5. Interactions with Other Medicines and Other Forms of Interactions

The sections below provide information on substances for which data on drug interactions with COCs are available. There is little information available about the clinical effect of most drug interactions that may affect COCs. However, based on the known pharmacokinetic effects of these drugs, clinical strategies to minimise any potential adverse effect on contraceptive effectiveness or safety are suggested. Consult the approved product labelling of all concurrently used drugs to obtain further information about interactions with COCs or the potential for metabolic enzyme or transporter system alterations.

### Effects of Other Drugs on Hormonal Contraceptives

#### Substances Decreasing the Plasma Concentrations of COCs and Potentially Diminishing the Efficacy of COCs:

Table 4 includes substances that have demonstrated an important drug interaction with COCs.

**Table 4: Significant drug interactions involving substances that affect COCs**

<b>Metabolic Enzyme Inducers</b>	
Clinical effect	Concomitant use of COCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of COCs (see <i>section 5.2 Pharmacokinetic Properties</i> ).  Decreased exposure of the estrogen and/or progestin component of COCs may potentially diminish the effectiveness of COCs and may lead to contraceptive failure or an increase in breakthrough bleeding.
Prevention or management	Counsel women to use a non-hormonal method of contraception when enzyme inducers are used with COCs.  Continue non-hormonal methods of contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability.
Examples	Aprepitant, barbiturates, bosentan, carbamazepine, efavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, rufinamide, topiramate, products containing St. John's wort <sup>a</sup> , and certain protease inhibitors (see separate section on protease inhibitors below).



<sup>a</sup> Induction potency of St. John’s wort may vary widely based on preparation.

Substances Increasing the Systemic Exposure of COCs:

Co-administration of atorvastatin or rosuvastatin and COCs containing ethinylestradiol increase systemic exposure of ethinylestradiol by approximately 20 to 25 percent. Ascorbic acid and acetaminophen may increase systemic exposure of ethinylestradiol, possibly by inhibition of conjugation. CYP3A inhibitors such as azoles (e.g. fluconazole) or grapefruit juice may increase systemic exposure of the estrogen and/or progestin component of COCs.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors:

Significant decreases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with some HIV protease inhibitors (e.g. nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir), some HCV protease inhibitors (e.g. boceprevir and telaprevir), and some non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine).

In contrast, significant increases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with certain other HIV protease inhibitors (e.g. indinavir and atazanavir/ritonavir) and with other non-nucleoside reverse transcriptase inhibitors (e.g. etravirine).

**Effects of COCs on Other Drugs**

Table 5 provides significant drug interaction information for drugs co-administered with NEXTSTELLIS.

**Table 5: Significant drug interaction information for drugs co-administered with COCs**

<b>Lamotrigine</b>	
Clinical effect	<ul style="list-style-type: none"> <li>Concomitant use of COCs with lamotrigine may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation (see <i>section 5.2 Pharmacokinetic Properties</i>).</li> <li>Decreased systemic exposure of lamotrigine may reduce seizure control.</li> </ul>
Prevention or management	<ul style="list-style-type: none"> <li>Dose adjustment may be necessary. Consult the approved product labelling for lamotrigine.</li> </ul>
<b>Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy</b>	
Clinical effect	<ul style="list-style-type: none"> <li>NEXTSTELLIS did not have a significant impact on systemic exposure of thyroid-binding and CBG (see <i>section 4.4 Special Warnings and Precautions for Use</i>).</li> </ul>
<b>Other Drugs</b>	

<b>Lamotrigine</b>	
Clinical effect	<ul style="list-style-type: none"> <li>• Concomitant use of COCs may decrease systemic exposure of acetaminophen, morphine, salicylic acid, and temazepam.</li> <li>• Concomitant use with estrogen-containing COCs may increase systemic exposure of other drugs (e.g. cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).</li> <li>• There is a potential for an increase in serum potassium concentration in women taking NEXTSTELLIS with other drugs that may increase serum potassium concentration (for example, ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS (see <i>section 4.4 Special Warnings and Precautions for Use</i>).</li> </ul>
Prevention or management	<ul style="list-style-type: none"> <li>• The dosage of drugs that can be affected by this interaction may need to be increased. Consult the approved product labelling for the concomitantly used drug.</li> </ul>

*In vitro* studies indicated that E4 does not inhibit CYPs, UGTs or major drug transporters at clinically relevant concentrations. E4 did not cause notable induction of CYP1A2, 2B6 or 3A4 in cultured human hepatocytes. Accordingly, pharmacokinetic interactions caused by the E4 component of NEXTSTELLIS are not expected. E4 was identified as a substrate of P-glycoprotein and breast cancer resistance protein. See *section 5.2 Pharmacokinetic Properties – Metabolism*, and *section 5.2 Pharmacokinetic Properties – Excretion*.

### **Effect on Laboratory Tests**

The use of COCs may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

## **4.6. Fertility, Pregnancy and Lactation**

### **Effects on Fertility**

NEXTSTELLIS acts as a contraceptive. See *section 5.1 Pharmacodynamic Properties – Clinical Trials*.

### **Use in Pregnancy**

#### **Category B3**

Discontinue NEXTSTELLIS if pregnancy occurs as there is no reason to use hormonal contraceptives during pregnancy (see *section 4.3 Contraindications*). Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects following exposure to COCs before conception or during early pregnancy.

Placental transfer of E4, drospirenone and/or their metabolites is expected. Animal studies revealed severe adverse effects on embryofetal development with the individual components of NEXTSTELLIS, which are expected after hormonal exposure in those species.

Embryofetal lethality was observed with oral administration of E4 to pregnant rats and rabbits. This occurred at doses yielding systemic exposure levels below or only marginally above that of patients. E4 also increased fetal skeletal abnormalities and reduced fetal weight in rats, and impaired ossification in rabbits, occurring in conjunction with maternotoxicity, consistent with the drug's estrogenic activity. While E4 is a native estrogen present during pregnancy, NEXTSTELLIS therapy is seen to result in maternal systemic exposure beyond physiological levels, particularly during early gestation.

Administration of drospirenone in combination with ethinylestradiol in rats was also shown to cause embryoletality. There was no indication of treatment-related malformations with drospirenone in rats or rabbits. Feminisation of male fetuses was observed in rats with administration of drospirenone in the last third of pregnancy, consistent with drug's recognised anti-androgenic activity, and seen at doses yielding systemic exposure 8-13 fold that anticipated clinically (based on AUC).

## **Use in Lactation**

### Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. COCs can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing woman to use other methods of contraception until she discontinues breast-feeding (see *section 4.2 Dose and Method of Administration*). The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for NEXTSTELLIS and any potential adverse effects on the breast-fed child from NEXTSTELLIS or from the underlying maternal condition.

After oral administration of ethinylestradiol 30 µg/drospirenone 3 mg, about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a potential maximal daily dose of less than 1 µg drospirenone in an infant.

### **4.7. Effects on Ability to Drive and Use Machines**

NEXTSTELLIS has no influence on ability to drive and use machines.

### **4.8. Adverse Effects (Undesirable Effects)**

The following clinically significant adverse reactions with the use of COCs are discussed in *section 4.4 Special Warnings and Precautions for Use*:

- Serious cardiovascular events

- Vascular events
- Hyperkalaemia
- Liver disease
- Headache
- Irregular uterine bleeding

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one product cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in practice. In the second column of the table below, the data provided reflect the experience with the use of NEXTSTELLIS in two large prospective Phase 3 studies, one in Europe/Russia (C301) and one in North America (C302) (n = 3,632), assessing the prevention of pregnancy in women 16-50 years of age. The mean time of NEXTSTELLIS exposure was 317 and 257 days for the respective studies. The third column reflects the overall experience in 3 Phase 2 European studies and the large prospective Phase 3 studies (C201, C202 and ES-C02 pooled with C302 and C301) (n = 3,790). The study population was 27 years of age on average, with a mean BMI of 25 kg/m<sup>2</sup>. The racial distribution was 83% White; 11% Black; 3% Asian; and 3% Other. The mean time of NEXTSTELLIS exposure for all the pooled Phase 2 and 3 studies was 280 days.

**Table 6: Adverse reactions occurring in > 1% of women receiving NEXTSTELLIS in pooled Phase 2 and 3 studies**

Adverse Reaction	Total Pooled Phase 3 studies n = 3,632 (%)	Total Pooled Phase 2 and 3 Studies n = 3,790 (%)
Any treatment-related adverse reaction	986 (27.1)	1056 (27.9)
Metrorrhagia	160 (4.4)	162 (4.3)
Acne	112 (3.1)	122 (3.2)
Headache	109 (3.0)	123 (3.2)
Vaginal haemorrhage	103 (2.8)	103 (2.7)
Dysmenorrhea	85 (2.3)	92 (2.4)
Weight increased	74 (2.0)	75 (2.0)
Breast tenderness	64 (1.8)	67 (1.8)
Breast pain	60 (1.7)	79 (2.1)

<b>Adverse Reaction</b>	<b>Total Pooled Phase 3 studies n = 3,632 (%)</b>	<b>Total Pooled Phase 2 and 3 Studies n = 3,790 (%)</b>
Libido decreased	55 (1.5)	56 (1.5)
Nausea	48 (1.3)	52 (1.4)
Menorrhagia	51 (1.4)	51 (1.3)
Mood Swings	47 (1.3)	50 (1.3)

Adverse Reactions Leading to Study Discontinuation (Phase 3 Clinical Studies) (> 1%):

Of 3,632 women in two Phase 3 clinical studies for prevention of pregnancy in women 16-50 years of age, 7.7% discontinued due to treatment-related adverse reactions; the most frequent adverse reaction leading to discontinuation was metrorrhagia (1.1%).

Serious Adverse Events:

A total of 45 serious treatment-emergent adverse events (all serious adverse events emerging during the studies without regards to the relationship to the drug) was reported by 41 subjects (1.1%) included in the safety population. These include nine cases of spontaneous abortion, two cases of ectopic pregnancy, seven cases of psychiatric disorders, two cases of depression, one case of vascular disorder and one case of venous thrombosis.

**Reporting Suspected Adverse Effects**

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

**4.9. Overdose**

Overdose may cause nausea, vomiting and withdrawal bleeding in women. Drospirenone is a spironolactone analogue which has antimineralocorticoid properties. Therefore, serum potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic Properties

#### Mechanism of Action

COCs prevent pregnancy primarily by suppressing ovulation.

E4 is a naturally occurring estrogen produced by the human fetal liver. It is only produced during human pregnancy and reaches the maternal circulation through the placenta. The E4 in NEXTSTELLIS is synthesised from a plant source. E4 displays a high selectivity for estrogen receptors (ERs) and binds to both ER $\alpha$  and ER $\beta$ , with a 4 to 6 times higher affinity for ER $\alpha$  compared to ER $\beta$ . Estrogen agonist activity by E4 was demonstrated in various cell-based assays *in vitro* and animal models *in vivo*. E4 differs from ethinylestradiol by the lack of an ethinyl group in the 17-alpha position. In humans, E4 is an end-product of steroid metabolism and is not reconverted to estriol, estradiol or estrone.

The progestin drospirenone possesses antigonadotropic, antiandrogenic and mild antimineralocorticoid properties and has no estrogenic, glucocorticoid or antiglucocorticoid activity. These properties are pharmacologically similar to the natural hormone progesterone.

#### Clinical Trials

To evaluate the effects on ovarian function inhibition of E4/drospirenone and the ethinylestradiol 20  $\mu$ g/drospirenone 3 mg combination, a clinical study compared levels of hormone markers (i.e. luteinizing hormone, follicle-stimulating hormone, estradiol, progesterone), endometrial thickness, return to fertility, as well as safety and tolerability. Ovarian function was adequately suppressed in both groups. There was no difference between the E4/drospirenone and ethinylestradiol/drospirenone treatment groups observed for endometrial thickness during the entire study. Return to ovulation was demonstrated for both COCs and occurred on average 15.5 and 18.1 days after intake of the last (inactive) tablet, for E4/drospirenone and ethinylestradiol/drospirenone, respectively.

#### Drug Interaction Studies

See *Effects of Combined Oral Contraceptives on Other Drugs* for *in vitro* studies evaluating E4 inhibition of CYP enzymes.

#### *Effects of Other Drugs on Combined Oral Contraceptives Substances Diminishing the Efficacy of COCs*

An open-label crossover, clinical drug-drug interaction study was performed with E4/drospirenone and valproic acid, an *in vivo* inhibitor of UGT2B7, to assess the clinical impact of UGT2B7 inhibition on exposure to E4, drospirenone and E4-glucuronide metabolites. Co-administration of the strong UGT2B7 inhibitor valproic acid with

E4/drospirenone for 12 days increased the AUC<sub>(0-∞)</sub> and C<sub>max</sub> of E4 1.13 and 1.36 fold, respectively, and did not impact drospirenone. These changes are considered of no clinical relevance.

### Pregnancy Prevention

The efficacy of E4/drospirenone was evaluated in two prospective, multicentre, open-label, single-arm studies, one in Europe/Russia (NCT02817828; C301) and one in North America (NCT02817841; C302). The efficacy population of the C301 was 1,313 women 18-35 years of age with 13,692 at-risk cycles, i.e. cycles with confirmed sexual intercourse and without use of non-hormonal methods of contraception. The efficacy population for the C302 study was 1,524 women 16-35 years of age with 12,763 at-risk cycles. In the European study the mean age was 25.0 years and mean BMI 22.88 kg/m<sup>2</sup> and 98.6% were Caucasian, 0.6% Black, 0.7% Asian and 0.1% other. In the North American study, the mean age was 25.8 years and mean BMI 25.76 kg/m<sup>2</sup> and women with a BMI ≥ 30 kg/m<sup>2</sup> and ≤ 35 kg/m<sup>2</sup> accounted for 23% of the study population. 70.1% were Caucasian, 19.5% Black or African American, 4.8% Asian, 0.9% American Indian or Alaska native, 0.4% Native Hawaiian or other Pacific Islander and 4.2% other.

In C301, there were 5 on-treatment pregnancies that occurred in women aged 16 to 35 years, leading to a Pearl Index<sup>1</sup> (95% CI) of 0.47 (0.15, 1.11). In C302, there were 20 on-treatment pregnancies in women with BMI ≤ 35 kg/m<sup>2</sup> and 6 on-treatment pregnancies in women with BMI ≥ 30 kg/m<sup>2</sup>, leading to an overall Pearl Index of 2.65 (1.73-3.88). Women with a BMI ≥ 30 kg/m<sup>2</sup> and ≤ 35 kg/m<sup>2</sup> accounted for 23% of the C302 study population.

The Pearl Indices reported in C301 and C302 are consistent with the Trussell J & Portman D 2013<sup>2</sup> efficacy charts.

In a pooled analysis of both C301 and C302, the combined efficacy population was 2,837 women with 26,455 at-risk cycles. There were 31 on-treatment pregnancies that occurred in women ≤ 35 years, leading to a Pearl Index (95% CI) of 1.52 (1.04, 2.16).

**Table 7: Pearl index based on at-risk cycles and reported pregnancies in women ≤ 35 years of age in studies C301 (Europe and Russia) and C302 (USA and Canada)**

	<b>NEXTSTELLIS C301 (n = 1,313)</b>	<b>NEXTSTELLIS C302 (n = 1,524)</b>
Subjects with pregnancy, n (%)	5	26

<sup>1</sup> The Pearl Index (PI) is defined as the number of pregnancies divided by the exposure time in woman years (WY) multiplied by 100.

<sup>2</sup> Trussell J & Portman D (2013). The Creeping Pearl: Why Has the Rate of Contraceptive Failure Increased in Clinical Trials of Combined Hormonal Contraceptive Pills? *Contraception*. Nov; 88(5): 604-610. doi:10.1016/j.contraception.2013.04.001.

	<b>NEXTSTELLIS C301 (n = 1,313)</b>	<b>NEXTSTELLIS C302 (n = 1,524)</b>
Total number of evaluable at-risk cycles	13,692	12,763
Pearl Index for evaluable at-risk cycles	0.47	2.65
95% Confidence Interval for Pearl Index, Lower Limit, Upper Limit	0.15, 1.11	1.73, 3.88

### Effect on Bleeding Patterns

The bleeding pattern with NEXTSTELLIS was assessed systematically using patient diaries in Studies C301 and C302 and was characterised by predictable withdrawal bleeds and low occurrence of bleeding irregularities (see *section 4.4 Special Warnings and Precautions for Use*).

**Table 8: Adult women with scheduled and unscheduled bleeding or spotting**

	<b>Scheduled</b>				<b>Unscheduled</b>			
	C301	C301	C302	C302	C301	C301	C302	C302
Cycle	n/N <sup>1</sup>	Rate (%)	n/N <sup>1</sup>	Rate (%)	n/N <sup>1</sup>	Rate (%)	n/N <sup>1</sup>	Rate (%)
1	1423/1507	94.43	1528/1758	86.92	354/1507	23.49	532/1758	30.26
6	1240/1331	93.16	1094/1319	82.94	207/1331	15.55	253/1319	19.18
12	1089/1183	92.05	872/1006	86.68	154/1183	13.02	175/1006	17.40

<sup>1</sup>Abbreviations: n = number of subjects with bleeding or spotting; N = number of subjects with cycle data

In studies C301 and C302, a total of 54 and 48 women (3.4% and 2.6%), respectively, discontinued from these studies of NEXTSTELLIS due to problems with unscheduled bleeding or amenorrhea.

## **5.2. Pharmacokinetic Properties**

### **Absorption**

E4 is rapidly absorbed after ingestion. After this initial absorption phase, lower secondary reabsorption peaks are observed in line with enterohepatic recycling. E4 plasma levels do not show any relevant deviation from dose-proportionality over the 15-75 mg estetrol monohydrate dose range, after single administration as well as in steady-state conditions for 14 days. After intake of NEXTSTELLIS, average peak plasma concentrations ( $C_{max}$ ) of 17.9 ng/mL are reached 0.5-2 hours after multiple ingestions of E4. Steady state is achieved after 4 days. Plasma drospirenone accumulates by a factor of about 1.6 following multiple dose administration of E4/drospirenone, as estimated from the daily area under the curve (AUC).



An open-label, single-dose, randomised, two-period, two-treatment, two-way crossover, comparative bioavailability study between a COC containing E4/drospirenone and a COC containing ethinylestradiol 20 µg/drospirenone 3 mg in healthy female volunteers was performed to compare the rate and extent of absorption of drospirenone.

The maximum concentration ( $C_{max}$ ),  $AUC_{0-t}$ , and  $AUC_{0-inf}$  of drospirenone in E4/drospirenone were 35 ng/mL, 453 ng.h/mL, and 504 ng.h/mL. The maximum concentration ( $C_{max}$ ),  $AUC_{0-t}$ , and  $AUC_{0-inf}$  of drospirenone in ethinylestradiol/drospirenone were 36 ng/mL, 493 ng.h/mL, and 556 ng.h/mL.

### Food Effect

The effect of a high fat meal on the bioavailability of E4 and drospirenone was evaluated following a single oral administration of E4/drospirenone in fasted and in fed conditions. Food decreased the peak absorption of E4 and drospirenone ( $C_{max}$ ) while it did not affect their extent of exposure (AUC) following oral administration of a single E4/drospirenone. Food effect on  $C_{max}$  was more pronounced for the absorption of E4 (the  $C_{max}$  ratio of Geometric Least Squares Mean for E4 was 0.51) than for the absorption of drospirenone (the  $C_{max}$  ratio of Geometric Least Squares Mean for DR drospirenone SP was 0.75), and was clinically significant, with the 90% CIs outside the 80% to 125% acceptance range (0.37; 0.70 for E4 and 0.66; 0.84 for drospirenone). The peak concentration of E4 and drospirenone was also reached sooner in fasted conditions than in fed conditions.

### **Distribution**

E4 is moderately bound by human plasma proteins (45.5%-50.4%) and human serum albumin (58.6%), and low binding to human  $\alpha_1$ -acid glycoprotein (11.2%). E4 does not bind to SHBG. E4 does not preferentially partition into blood cells.

After oral administration, serum drospirenone levels decrease in two phases which are characterised by half-lives of  $1.6 \pm 0.7$  h and  $27.0 \pm 7.5$  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  $3.7 \pm 1.2$  L/kg.

### **Metabolism**

After oral administration of 15 mg estetrol monohydrate alone, E4 undergoes extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The contribution of hepatic CYPs to the metabolism of E4 is very limited; instead, UGT2B7 and SULT1E1 play major roles. Pharmacokinetic data demonstrate that most of the E4 is bioavailable and is excreted in the urine as sulphate and glucuronide conjugates in contrast to other estrogens, which are mainly excreted through the bile. The glucuronide metabolites of E4 were shown to possess negligible estrogenic activity.

Drospirenone is extensively metabolised after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalysed by CYP3A4 and has demonstrated a capacity to inhibit this enzyme and CYP1A1, CYP2C9 and CYP2C19 *in vitro*.

### **Excretion**

The terminal elimination half-life of E4 was observed around 24 hours under steady-state conditions. Following administration of a single oral solution of 15 mg [<sup>14</sup>C]-estetrol (monohydrate), approximately 70% of the total recovered radioactivity was detected in urine as glucuronide and sulphate conjugated metabolites and 22% in faeces as unconjugated E4.

The metabolic clearance rate of drospirenone in serum is  $1.5 \pm 0.2$  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 hours.

## **5.3. Preclinical Safety Data**

### **Genotoxicity**

E4 is not considered to be genotoxic based on the weight of evidence from a set of *in vitro* and *in vivo* studies, comprising assays for mutagenicity in bacterial and mammalian cells, and the rat bone marrow micronucleus test and Comet assay.

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

### **Carcinogenicity**

Carcinogenicity studies have not been performed with E4 and drospirenone in combination.

In a 2-year oral carcinogenicity study with E4 in mice, an increase of uterine and cervix neoplasms was found at  $\geq 0.25$  mg/kg/day and of mammary gland and pituitary gland at 1 mg/kg/day. Systemic exposure in animals at these doses was 1.4-6 times lower than in patients treated with NEXTSTELLIS (based on plasma AUC). In a similar study in rats, E4 caused an increased incidence of mammary gland neoplasms (adenocarcinoma) with dosing at 0.8 mg/kg/day, yielding systemic exposure around half that of patients. The tumours observed in rodents after E4 treatment are consistent with its estrogenic

properties. Rodents are recognised to be particularly sensitive to the development of tumours following hormonal perturbation.

Long-term carcinogenicity studies were performed in mice and rats with drospirenone. After 2 years oral treatment of mice and rats, there were no increases in the incidence of neoplastic lesions. Exposure to drospirenone (based on AUC) was up to 3-fold (mice) and 8-fold (rats) than that anticipated in humans at the recommended clinical dose.

It should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tumours. Long-term animal studies however, did not definitively indicate a tumourigenic potential for the clinical use of either drospirenone or estetrol.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of Excipients**

Active tablet: Lactose monohydrate, sodium starch glycollate type A, maize starch, povidone and magnesium stearate; film-coating: AquaPolish Pink 044.08 MS (hypromellose, hyprollose, purified talc, hydrogenated cottonseed oil, titanium dioxide and iron oxide red).

Inactive tablet: StarLac (lactose monohydrate and maize starch) and magnesium stearate; film-coating: AquaPolish White 014.17 MS (hypromellose, hyprollose, purified talc, hydrogenated cottonseed oil and titanium dioxide).

### **6.2. Incompatibilities**

See *section 4.5 Interactions with Other Medicines and Other Forms of Interactions*.

### **6.3. Shelf Life**

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

### **6.4. Special Precautions for Storage**

Store below 30°C.

### **6.5. Nature and Contents of Container**

NEXTSTELLIS is supplied in PVC/aluminium blister packs, each containing 24 film-coated pink tablets and 4 film-coated white tablets.

NEXTSTELLIS is supplied in cardboard cartons containing 1, 3 or 6 blister packs as provided below:

1 blister pack (1 x 28 tablets)

3 blister packs (3 x 28 tablets)

6 blister packs (6 x 28 tablets)

Physician sample pack, 1 blister pack (1 x 28 tablets)

Not all pack sizes may be marketed.

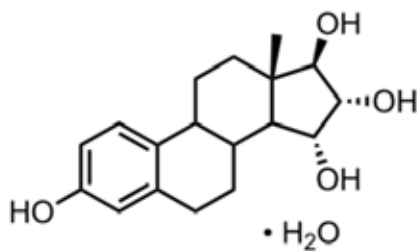
## 6.6. Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6.7. Physicochemical Properties

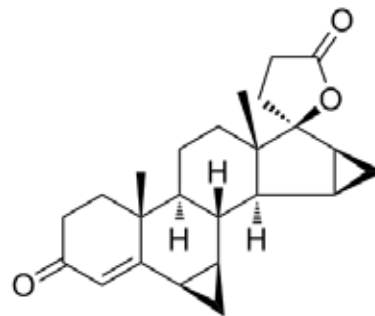
### Chemical Structure

Estetrol monohydrate



C<sub>18</sub>H<sub>24</sub>O<sub>4</sub>·H<sub>2</sub>O

Drospirenone



C<sub>24</sub>H<sub>30</sub>O<sub>3</sub>

### CAS Number

Estetrol monohydrate: 2055649-81-3

Drospirenone: 67392-87-4

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8. SPONSOR

Mayne Pharma International Pty Ltd

ABN 88 007 870 984

1538 Main North Road

Salisbury South, SA 5106

Attachment AusPAR - Nextstellis - estetrol monohydrate/drospirenone - Mayne Pharma International Pty Ltd - PM-2020-04185-1-5 Final 21 July 2022. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

[maynepharma.com.au](http://maynepharma.com.au)

**9. DATE OF FIRST APPROVAL**

26 November 2021

**10. DATE OF REVISION**

Not applicable

**SUMMARY TABLE OF CHANGES**

Section changed	Summary of new information