SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE
ZOELY® 2,5 mg/1,5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
White active tablets: Each tablet contains 2,5 mg nomegestrol acetate and 1,5 mg estradiol (as hemihydrate).
Yellow placebo tablets: These tablets do not contain active substances.

Contains sugar.
Each white active film-coated tablet contains 57,71 mg of lactose monohydrate.
Each yellow placebo film-coated tablet contains 61,76 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.

The active film-coated tablets are white, round and 5,5 mm in diameter. They are coded ‘ne’ on both sides.
The placebo film-coated tablets are yellow, round and 5,5 mm in diameter. They are coded ‘p’ on both sides.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Oral contraception.

4.2 Posology and method of administration
Posology
Tablets must be taken orally every day at about the same time without regard to meals, with some liquid as needed, and in the order as directed on the package. One tablet is to be taken daily for 28 consecutive days. Each pill pack starts with 24 white active tablets followed by 4 yellow placebo tablets (see **Picture 1**). A subsequent pack is started immediately after finishing the previous pack, without a break in daily tablet intake and irrespective of presence or absence of withdrawal bleeding. Withdrawal bleeding usually starts on day 2 to 3 after intake of the last white tablet and may not have finished before the next pack started.

How to start ZOELY
No preceding hormonal contraceptive use
Tablet-taking has to start on day 1 of the woman’s natural cycle (i.e., the first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary. Starting on days 2 to 5 is allowed, but during the first pill pack a barrier contraceptive method should be used until the woman has completed 7 days of uninterrupted white tablet-taking (see **Picture 1**).

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)
The woman should start with ZOELY preferably on the day after the last tablet containing the active substance of her previous COC, but at least on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch was used, the woman should start using ZOELY preferably on the day of removal, but at least

when the next application would have been due.

If the woman has been using her previous method consistently and correctly, and if it is reasonably certain that she is not pregnant, she may also switch on any day. The hormone-free interval of the previous method should never be extended beyond its recommended length.

Changing from a progestogen-only-method (minipill, implant, injectable) or from a hormone-medicated Intra-Uterine System (IUS)
The woman may switch on any day from the minipill and ZOELY should be started on the next day. An implant or IUS may be removed on any day, and ZOELY should be started on the day of its removal.

When changing from an injectable, ZOELY should be started on the day when the next injection would have been due. In all of these cases, the woman should be advised to additionally use a barrier method until she has completed 7 days of uninterrupted white active tablet-taking.

Following first-trimester abortion
The woman may start ZOELY immediately. When doing so, no additional contraceptive measures are necessary.

Following delivery or second-trimester abortion
For breastfeeding women (see section 4.6).

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

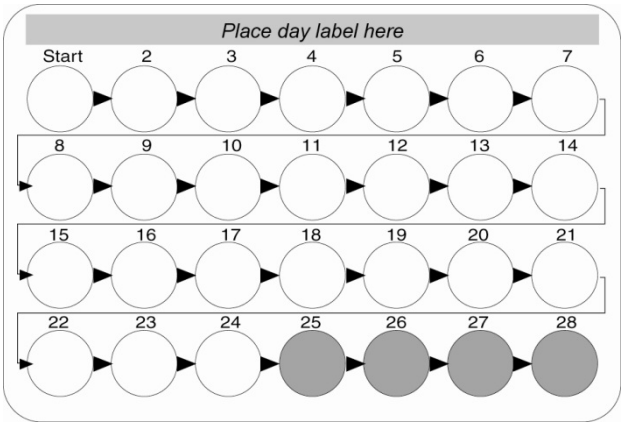
The increased risk of venous thromboembolism (VTE) during the postpartum period should be considered when restarting ZOELY (see section 4.4).

Management of missed tablets
The following advice only refers to missed white active tablets: If user is **less than 24 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 the subsequent tablets at the usual time.

If she is **24 or more hours** late in taking any active tablet, contraceptive protection may be reduced.

The management of missed tablets can be guided by the following two basic rules:
- 7 days of uninterrupted ‘white active tablet’-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.
- The more ‘white active tablets’ are missed and the closer the missed tablets are to the 4 yellow placebo tablets, the higher the risk of a pregnancy.

Picture 1



Day 1 to 7
The user should take the last missed white tablet as soon as she remembers, even if this means taking 2 tablets at the same time. She then continues to take tablets at her usual time. A barrier contraceptive method should be used until she has completed 7 days of uninterrupted white tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

Day 8 to 17
The user should take the last missed white tablet as soon as she remembers even if this means taking 2 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 additional contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use additional contraceptive precautions until she has completed 7 days of uninterrupted white tablet-taking.

Day 18 to 24
The risk of reduced reliability is higher because of the forthcoming yellow placebo-tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use additional 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, she should follow the first of these two options and use additional precautions for the next 7 days as well.

Option 1: The user 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 the active tablets are used up. The 4 placebo tablets from the last row must be discarded. The next blister pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on the tablet-taking days.

Option 2: The women may be advised to discontinue active tablet–taking from the current blister pack. She should then take placebo tablets from the last row for a maximum of 3 days, such that the total number of placebo plus missed active white tablets is not more than 4, and subsequently continue with the next blister pack.
If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet phase, the possibility of a pregnancy should be considered.
Please note: If the user is not sure about the number or colour of tablets missed and what advice to follow, a barrier contraceptive method should be used until she has completed 7 days of uninterrupted white active tablet-taking.

Yellow placebo tablets missed
Contraceptive protection is not reduced. Yellow tablets from the last (4th) row of the blister can be disregarded. However, the missed tablets should be discarded to avoid unintentionally prolonging the placebo tablet phase.

Advice in case of gastrointestinal disturbances
In case of severe gastrointestinal disturbance (e.g., vomiting or diarrhoea), absorption of the active substances may not be complete and additional contraceptive measures should be used.

If vomiting occurs within 3 to 4 hours after white tablet-taking, the tablet should be considered as missed and a new tablet should be taken as soon as possible. The new tablet should be taken within 24 hours of the usual time of tablet-taking if possible. The next tablet should then be taken at the usual time. If 24 or more hours have passed since last tablet intake, the advice concerning missed tablets as given (see 'Management of missed tablets'), is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra white tablet(s) from another pack.

How to shift periods or how to delay a period
To delay a period the woman should continue with another blister pack of ZOELY without taking the yellow tablets from her current pack. The extension can be carried on until the end of the white tablets in the second pack.

Regular intake of ZOELY is then resumed after the yellow placebo tablets of the second pack have been taken. During the extension period the woman may experience breakthrough-bleeding or spotting.

To shift her periods to another day of the week than the woman's current scheme, she may be advised to shorten her forthcoming placebo tablet phase by a maximum of 4 days. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and may experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

4.3 Contraindications
ZOELY should not be used in the presence of any of the conditions listed below. Should any of the following conditions appear for the first time during ZOELY use, the product should be stopped immediately:

- Hypersensitivity to any of the active substances of ZOELY or to any of the other excipients listed in section 6.1.
- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism - current VTE (on anticoagulants) or history of (e.g., deep venous thrombosis (DVT), or pulmonary embolism (PE)).
  - Known hereditary or acquired predisposition for venous thromboembolism, such as activated protein C (APC)-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
  - Major surgery with prolonged immobilisation (see section 4.4).
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).
- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism - current ATE, history of ATE (e.g., myocardial infarction) or prodromal condition (e.g., angina pectoris).
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g., transient ischaemic attack (TIA)).

- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) 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 hypertriglyceridaemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts).
- Meningioma or history of meningioma.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy (see section 4.6).

4.4 Special warnings and precautions for use
The decision to prescribe ZOELY should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with ZOELY compares with other combined hormonal contraceptives (CHCs) (see sections 4.3 and 4.4).

If any of the conditions or risk factors mentioned below is present, the suitability of ZOELY should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her medical practitioner to determine whether the use of ZOELY should be discontinued. All data presented below are based upon epidemiological data obtained with combined hormonal contraceptives (CHCs) containing ethinylestradiol and apply to ZOELY.

Depression and mood changes
Mood changes and depression are side effects reported with the use of hormonal containing products including ZOELY (see section 4.8). There is some evidence that the use of estrogen and/or progesterone/progestogen containing medicines may be associated with severe depression and a higher risk of suicidal thoughts/behaviours (e.g., talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs doing self-destructive things, personality changes) and suicide.

Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with ZOELY.

Risk of venous thromboembolism (VTE)
- The use of combined hormonal contraceptives (CHCs) such as ZOELY carries an increased risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. ZOELY may have a risk of VTE in the same range as observed with CHC containing levonorgestrel. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, how her current**

risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

- In women who do not use a CHC and are not pregnant about 2 out of 10 000 will develop a VTE over the period of one year. However, in any individual woman, the risk may be far higher, depending on her underlying risk factors (see below).
- Epidemiological studies in women who use low dose (< 50 micrograms ethinylestradiol) CHC have found that out of 10 000 women between 6 and 12 will develop a VTE in one year.
- It is estimated that out of 10 000 women who use a levonorgestrel-containing CHC about 6 will develop a VTE in one year. This is based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2,3 to 3,6.
- The number of VTEs per year with low dose CHCs such as ZOELY is fewer than the number expected in women during pregnancy or in the postpartum period.
- VTE may be fatal in 1 to 2 % of cases.
- Thrombosis has also been reported to occur in the other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in users of CHCs such as ZOELY.

Risk factors for VTE
The risk for venous thromboembolic complications in users of CHC's such as ZOELY, may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table below).

ZOELY is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative, a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: Temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if ZOELY has not been discontinued in advance (see section 4.3).
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age, e.g., before 50)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in the 6-week period of the puerperium, must be considered (see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
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 CHC such as ZOELY.

Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- 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.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs such as ZOELY with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g., transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table below). ZOELY is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC such as ZOELY should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors

Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g., below 50)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use, such as ZOELY.
Migraine	An increase in frequency or severity of migraine during CHC use such as ZOELY (which may be prodromal of a cerebrovascular event), may be a reason for immediate discontinuation of ZOELY.
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

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 CHC such as ZOELY.

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 transient ischaemic attack (TIA).

Symptoms of a myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Tumours
- The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Long-term use of ethinylestradiol-containing COCs may contribute to this increased risk of cervical cancer.
- With the use of the higher-dosed COCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to ZOELY remains to be confirmed.
- 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 estrogen-containing COCs such as ZOELY.
- In another epidemiological study of 1,8 million Danish women followed an average of 10,9 years, the reported RR of breast cancer among COC users increased with longer duration of use compared with women who never used COCs (overall RR = 1,19; RR ranged from 1,17 for 1 to less than 5 years of use to 1,46 after more than 10 years of use). The reported absolute risk difference (number of breast cancer cases between never-users compared with current and recent COC users) was small: 13 per 100 000 woman-years.
- Epidemiological 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.
- Benign and even more rarely, malignant liver tumours have been reported in users of

COCs such as ZOELY. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, a hepatic 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.

Meningioma
The occurrence of meningiomas (single and multiple) has been reported in association with use of nomegestrol acetate such as ZOELY, especially at high doses and for prolonged use (several years). Patients should be monitored for signs and symptoms of meningiomas in accordance with clinical practice. If a patient is diagnosed with meningioma, any nomegestrol acetate-containing treatment, must be stopped, as a precautionary measure (see section 4.3).

There is some evidence that the meningioma risk may decrease after treatment discontinuation of nomegestrol acetate such as ZOELY.

Hepatitis C
During clinical trials with the Hepatitis C virus (HCV) combination medicine regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medications containing estrogens other than ethinylestradiol, such as estradiol had a rate of ALT elevation similar to those not receiving any estrogens. Caution is warranted for co-administration with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

Other conditions
- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs such as ZOELY.
- Although, increases in blood pressure have been reported in many women taking COCs, such as ZOELY, 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 prescriber to suspend the intake of the tablets 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 estrogen-containing COC use such as ZOELY: 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.
- Exogenous estrogens contained in COCs such as ZOELY, may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of ZOELY 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 such as ZOELY.
- Although COCs such as ZOELY 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 ZOELY. Diabetic women should be carefully observed while taking a COC, especially in the first months of use.
- Crohn's disease, ulcerative colitis, and worsening of depression have been associated with COC use.
- Chloasma may 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 ZOELY.

Medical examination/consultation
Prior to the initiation or reinstitution of ZOELY use a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of ZOELY compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the patient information leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy
The efficacy of ZOELY may be reduced in the event of e.g., missed tablets (see section 4.2), gastrointestinal disturbances during active tablet taking (see section 4.2), or use of concomitant medication that decrease the plasma concentrations of nomegestrol acetate (see section 4.5).

Cycle control
Breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaption interval of about 3 cycles. The percentage of women using ZOELY experiencing intracyclic bleeding after this adaptation period ranged from 15 to 20 %. 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.

The duration of withdrawal bleeding in women using ZOELY is on average 3 to 4 days. Users of ZOELY may also miss their withdrawal bleeding although not pregnant. Early bleeding patterns (cycles 2 to 4) are predictive of future bleeding patterns.

If absence of withdrawal bleeding occurs and ZOELY has been taken according to the instructions as described in section 4.2, it is unlikely that the woman is pregnant. If ZOELY has not been taken as directed or if 2 consecutive withdrawal bleedings are missed, pregnancy must be ruled out before ZOELY is continued.

Excipients
ZOELY contains < 60 mg lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

4.5 Interaction with other medicines and other forms of interactions
Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

Influence of other medicines on ZOELY
Interactions between ZOELY and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature for COCs

in general:

Hepatic metabolism: Interactions can occur with medicines or herbal products that induce cytochrome P450 enzymes (CYP) which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including ZOELY. These products include anticonvulsants (e.g., carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate); anti-infective medicines (e.g., rifampicin, rifabutin, griseofulvin); St. John's wort; bosentan and HIV or Hepatitis C virus (HCV) protease inhibitors (e.g., ritonavir, nelfinavir boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz). The net effect of these changes may be clinically relevant in some cases.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After medicine therapy is discontinued, enzyme induction can last for about 28 days.

Women receiving any of the above-mentioned hepatic enzyme-inducing medicines or herbal products should be advised that the efficacy of ZOELY may be reduced. A barrier contraceptive method should also be used during administration of the hepatic enzyme-inducing medicine, and for 28 days after discontinuation of the hepatic enzyme-inducing medicines.

If concomitant medicine administration runs beyond the end of the active tablets in the current blister pack, the next blister pack should be started right away without the usual placebo tablet interval.

For women on long-term therapy with hepatic enzyme-inducing medicines, an alternative method of contraception unaffected by enzyme-inducing medicines should be considered.

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A inhibitors may increase the serum concentrations of estrogens or progestins.

Interaction studies were not performed with ZOELY, but 2 studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed nomegestrol acetate-estradiol combination (nomegestrol acetate 3,75 mg + 1,5 mg estradiol) in post-menopausal women.

Concomitant use of rifampicin decreases the $AUC_{0-\infty}$ of nomegestrol acetate by 95 % and increases the $AUC_{0-tlast}$ of estradiol by 25 %. Concomitant use of ketoconazole (200 mg single dose) does not modify estradiol metabolism whereas increases in the peak concentration (85 %) and $AUC_{0-\infty}$ (115 %) of nomegestrol acetate were observed, which were of no clinical relevance. Similar conclusions are expected in women of childbearing potential.

Women using rifamycins such as rifampicin, rifabutin and rifapentine should use additional contraceptive measures.

Influence of ZOELY on other medicines
ZOELY may affect the metabolism of other medicines.

Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine). Contraceptives containing ethinylestradiol such as ZOELY may decrease the concentrations of lamotrigine by approximately 50 %. Attention should be paid, notably when introducing a combined contraceptive, even with estradiol, in a well-equilibrated

woman given lamotrigine.

Other interactions
During clinical trials with the Hepatitis C virus (HCV) combination medicine regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. Women using medicines containing estrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any estrogens. Caution is warranted for co-administration with the combination medicine regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

Laboratory tests
The use of COCs such as ZOELY may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Fertility, pregnancy and lactation
Pregnancy
ZOELY is not indicated during pregnancy (see section 4.3).

If pregnancy occurs during treatment with ZOELY, further intake should be stopped.

The increased risk of VTE during the postpartum period should be considered when re-starting ZOELY (see sections 4.2 and 4.4).

Lactation
ZOELY should not be used until the breastfeeding mother has completely weaned her child. An alternative contraceptive method should be proposed to women wishing to breastfeed.

Lactation may be influenced by COCs such as ZOELY as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

Fertility
ZOELY is indicated for the prevention of pregnancy.

4.7 Effects on ability to drive and use machines
ZOELY has no influence on the ability to drive and use machines.

4.8 Undesirable effects
Summary of the safety profile
Seven multi-centre clinical trials of up to 2 years duration were used to evaluate safety of ZOELY. In total 3 490 women, aged 18 to 50, were enrolled and completed 35 028 cycles.

An increased risk for venous and arterial thromboembolism, causative of serious adverse events has been observed with the use of CHCs (see section 4.4)

Tabulated list of adverse reactions
Possibly related undesirable effects that have been reported in users of ZOELY are listed in the table below.

All adverse reactions are listed by system organ class and frequency: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1 000 to < 1/100) and Rare (≥ 1/10 000) to < 1/1 000).

	Adverse Reactions in MedDRA Term[1]			
Body system	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000) to < 1/1 000)**
Metabolism and nutrition disorders			Increased appetite, fluid retention	Decreased appetite
Psychiatric disorders		Decreased libido, depression/ depressed mood, mood altered		Increased libido
Nervous system disorders		Headache, migraine		Cerebrovascular accident, transient ischaemic attack, disturbance in attention
Eye disorders				Dry eye, contact lens intolerance
Vascular disorders			Hot flushes	Venous thromboembolism
Gastrointestinal disorders		Nausea	Abdominal distension	Dry mouth
Hepatobiliary disorders				Cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	Acne[2]		Hyperhidrosis, alopecia, pruritus, dry skin, seborrhoea	Chloasma, hypertrichosis
Musculoskeletal and connective tissue disorders			Sensation of heaviness	
Reproductive system and breast disorders	Abnormal withdrawal bleeding	Metrorrhagia, menorrhagia, breast pain, pelvic pain	Hypomenorrhea, breast swelling, galactorrhoea, uterine spasm, premenstrual syndrome, breast mass, dyspareunia, vulvovaginal dryness	Vaginal odour, vulvovaginal discomfort
General disorders and administrative site conditions			Irritability, oedema	Hunger

Investigations		Increased weight	Increased hepatic enzyme	

[1] The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.
[2] Acne was a solicited rather than spontaneously reported event, being assessed at every study visit.

Description of selected adverse reactions
Vascular disorders
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs such as ZOELY, which are discussed in more detail in section 4.4.

Immune system disorders
Hypersensitivity reactions (anaphylactic shock, angioedema, dyspnoea, eyelid oedema, erythema, gingival swelling, lip swelling, paraesthesia, oral rash, swollen tongue and urticaria) have been reported in ZOELY users (frequency unknown).

Post-marketing reported side effects
The following side effects have been reported with post-marketing use of estrogen and/or progesterone/progestogen-containing medicines: Severe depression with a higher risk of suicidal thoughts/behaviours and suicide.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://sahpra.org.za/Publications/Index/8.

4.9 Overdose
Multiple doses up to 5 times the daily dose of ZOELY and single doses up to 40 times the daily dose of nomegestrol acetate alone have been used in women without safety concern.

On the basis of general experience with combined oral contraceptives, symptoms that may occur are nausea, vomiting and, in young girls, slight vaginal bleeding (see section 4.8). There are no antidotes and treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A.18.8 Ovulation controlling agents
Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and estrogens, fixed combinations, ATC code: G03AA14.

Nomegestrol acetate is a progestogen derived from, and structurally similar to, the naturally occurring steroid hormone, progesterone. Nomegestrol acetate has an affinity for the progesterone receptor and has anti-gonadotropic activity, moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The estrogen contained in ZOELY is 17β-estradiol, a natural estrogen identical to the endogenous human 17β-estradiol. During use of 2,5 mg nomegestrol acetate and 1,5 mg estradiol the average 17β-estradiol levels are comparable to the 17β-estradiol levels during

the early follicular and late luteal phase of the menstrual cycle (see section 5.2).

Paediatric population
No data on efficacy and safety are available in adolescents below 18 years. Available pharmacokinetic data are described in section 5.2.

5.2 Pharmacokinetic properties
Nomegestrol acetate (NOMAC)
Absorption
After a single oral administration, nomegestrol acetate is absorbed and maximum plasma concentrations of nomegestrol acetate of about 7 ng/ml are reached at 2 hours. The absolute bioavailability of nomegestrol acetate after a single dose is 63 %. No clinically relevant effect of food was observed on the bioavailability of nomegestrol acetate.

Distribution
Nomegestrol acetate is extensively bound to albumin (97 to 98 %), but does not bind to sex-hormone binding globulin (SHBG) or corticoid-binding globulin (CBG). The apparent volume of distribution of nomegestrol acetate at steady-state is 1 645 ± 576 litre.

Metabolism
Nomegestrol acetate is metabolised into several inactive hydroxylated metabolites by liver cytochrome P450 enzymes, mainly CYP2C8, CYP2C19, CYP3A4 and CYP3A5. Nomegestrol acetate and its hydroxylated metabolites undergo extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The apparent clearance at steady-state is 26 litre/hour.

Elimination
The elimination half-life ($t_{1/2}$) is 46 h (ranging from 28 to 83 hours) at steady state. The elimination half-life of metabolites was not determined. Nomegestrol acetate is excreted via urine and faeces. Approximately 80 % of the dose is excreted in urine and faeces in 4 days. Excretion of nomegestrol acetate was nearly complete after 10 days and amounts excreted were higher in faeces than in urine.

Linearity
Dose-linearity was observed in the range 0,625 to 5 mg (assessed in fertile and post-menopausal women).

Steady-state conditions
The pharmacokinetics of nomegestrol acetate are not influenced by SHBG. Steady-state is achieved after 5 days. Maximum plasma concentrations of nomegestrol acetate of about 12 ng/ml are reached 1,5 hours after dosing. Average steady-state plasma concentrations are 4 ng/ml.

Interactions
In vitro, nomegestrol acetate causes no notable induction or inhibition of any cytochrome P450 enzymes and has no clinically relevant interaction with the P-gp transporter.

Estradiol (E2)
Absorption
17β-estradiol is subject to a substantial first-pass effect after oral administration. The absolute bioavailability is approximately 5 %. No clinically relevant effect of food was observed on the bioavailability of 17β-estradiol.

Distribution
The distribution of exogenous and endogenous 17β-estradiol is similar. Estrogens are widely

distributed in the body and are generally found in higher concentrations in the sex-hormone target organs. Estradiol circulates in the blood bound to SHBG (37 %) and to albumin (61 %), while only approximately 1 to 2 % is unbound.

Metabolism
Oral exogenous 17β-estradiol is extensively metabolised. The metabolism of exogenous and endogenous 17β-estradiol is similar. 17β-estradiol is rapidly transformed in the gut and the liver into several metabolites, mainly estrone (E1), which are subsequently conjugated and undergo entero-hepatic circulation. There is a dynamic equilibrium between E2, E1 and E1-Sulphate (E1S) due to various enzymatic activities including E2-dehydrogenases, sulfotransferases and aryl sulfatases. Oxidation of E1 and E2 involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra-hepatic), CYP3A4, CYP3A5 and CYP1B1 and CYP2C9.

Elimination
17β-estradiol is rapidly cleared from the circulation. Due to metabolism and entero-hepatic circulation, a large circulating pool of estrogen sulphates and glucuronides is present. This results in a highly variable elimination half-life of 17β-estradiol, which is calculated to be 8,4 ± 6,4 h, after intravenous administration.

Steady-state conditions
Maximum serum concentrations of 17β-estradiol are about 90 pg/ml and are reached 6 hours after dosing. Average serum concentrations are 50 pg/ml and these 17β-estradiol levels correspond with the early and late phase of a woman's menstrual cycle.

Special populations
Paediatric population
The pharmacokinetics of nomegestrol acetate (primary objective) after single oral dosing of nomegestrol acetate and 1,5 mg estradiol in healthy post-menarcheal female adolescents and adult subjects were similar. The exposure of estradiol (secondary objective) was similar in adolescents versus adult subjects during the first 24 hours, and lower after 24 hours. The clinical relevance of this result is unknown.

Effect of renal impairment
No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of nomegestrol acetate and 1,5 mg estradiol.

Effect of hepatic impairment
No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of nomegestrol acetate and 1,5 mg estradiol. However, steroid hormones may be poorly metabolised in women with impaired liver function.

5.3 Preclinical safety data
Repeat dose toxicity studies with estradiol, nomegestrol acetate or combination have indicated expected estrogenic and gestagen effects.

Reproductive toxicity studies performed with the combination have shown foetotoxicity which is consistent with estradiol exposure.

Genotoxicity and carcinogenicity studies were not conducted with the combination. Nomegestrol acetate is not genotoxic.

However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core (white active and yellow placebo film-coated tablets):
Lactose monohydrate
Microcrystalline cellulose (E460)
Crospovidone (E1201)
Talc (E553b)
Magnesium stearate (E572)
Colloidal silica anhydrous

Tablet coating (white active film-coated tablets):
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol
Talc (E553b)

Tablet coating (yellow placebo film-coated tablets):
Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Yellow iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.
Do not remove tablets from blister until required for use.

6.5 Nature and contents of container

ZOELY tablets are packed in PVC/aluminium blister (transparent PVC thermoforming film with aluminium lidding foil), packed in a printed cardboard box. Packed in pack sizes of 28 tablets (24 white active tablets and 4 yellow placebo tablets).

6.6 Special precautions for disposal and other handling

COC tablets including ZOELY no longer required should not be disposed via wastewater or the municipal sewage system. The hormonal active compounds in the tablet may have harmful effects if reaching the aquatic environment. The tablets should be returned to a pharmacy or disposed of in another safe way according to local requirements. These measures will help to protect the environment.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
45/18.8/0064

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02 October 2014

10. DATE OF REVISION OF THE TEXT
16 October 2023