PROFESSIONAL INFORMATION

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 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.
The active film-coated tablets are white, round and 5,5 mm in a 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.

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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 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 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.

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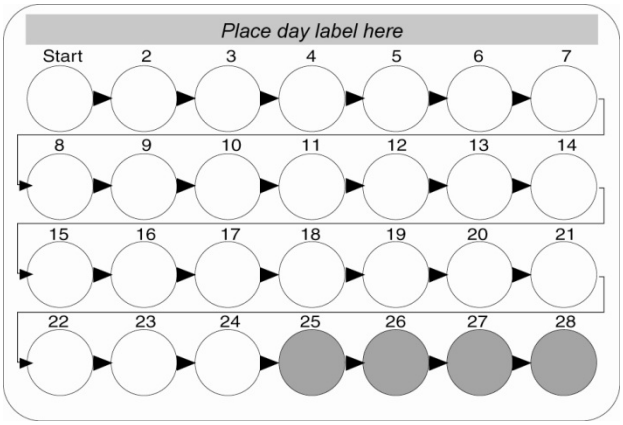
If she is **24 or more hours** late in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

- 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.
- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- The presence of severe or multiple risk factor(s) for venous or arterial thrombosis (see 4.4) such as:
  - diabetes mellitus with vascular symptoms
  - severe hypertension
  - severe dyslipoproteinaemia.
- Major surgery with prolonged immobilisation (see 4.4).
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C resistance, antithrombin-lll-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- 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).
- Known or suspected pregnancy (see 4.6).

4.4 Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of the use of ZOELY should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using ZOELY. In the event of aggravation, exacerbation or first

appearance of any of these conditions or risk factors, the woman should contact her medical practitioner.

Mood changes and depression are side effects reported with the use of hormonal containing products including ZOELY. There are some evidence that the use of oestrogen 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.

Circulatory Disorders

- The use of combined hormonal contraceptives (CHCs) such as ZOELY carries an increased risk of venous thromboembolism (VTE) compared with no use. The risk is also increased after initially starting a combined hormonal contraceptive or restarting the same or different combined hormonal contraceptive after a break in use of 4 weeks or more.
- Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use oestrogen-containing combined hormonal contraceptives is increased compared to non-users of combined oral contraceptives. VTE is fatal in 1 to 2 % of cases.
- Epidemiological studies have also associated the use of COCs with an increased risk for arterial thromboembolism (myocardial infarction, transient ischaemic attack).
- 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 combined hormonal contraceptive such as ZOELY (see 4.3).
- Symptoms of venous or arterial thrombosis or of a cerebrovascular accident can include: Unusual unilateral leg pain and/or swelling, sudden severe pain in the chest, whether or not it radiates to the left arm, sudden breathlessness, sudden onset of coughing, any unusual, severe, prolonged headache, sudden partial or complete loss of vision, diplopia, slurred speech or

aphasia, vertigo, collapse with or without focal seizure, weakness or very marked numbness suddenly affecting one side or one part of the body, motor disturbances, 'acute' abdomen.

- The risk of venous thromboembolic events increases with:
  - increasing age.
  - a positive family history of thromboembolism (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
  - prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least 4 weeks in advance) and not to resume until 2 weeks after complete remobilisation. Antithrombotic treatment should be considered if ZOELY use has not been discontinued in advance (see 4.3).
  - obesity (body mass index over 30 kg/m^2).
  - smoking.
- There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset of venous thrombosis.
- The risk of arterial thromboembolic complications or of a cerebrovascular accident increases with:
  - increasing age
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use ZOELY).
  - dyslipoproteinaemia
  - obesity (body mass index over 30 kg/m^2)
  - hypertension
  - migraine
  - valvular heart disease
  - atrial fibrillation

- a positive family history of arterial thrombosis (arterial thrombosis event in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use, as in ZOELY.

- Other medical conditions, which have been associated with adverse circulatory events, include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (see 4.6).
- An increase in frequency or severity of migraine during ZOELY use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of ZOELY use.

Women using COCs such as ZOELY should be specifically instructed to contact their medical practitioner in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, ZOELY use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (warfarin).

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 oestrogen-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.

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 oestrogens other than ethinylestradiol, such as estradiol had a rate of ALT elevation similar to those not receiving any oestrogens. 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 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.
- Increases in blood pressure have been reported in many women taking COCs, such as ZOELY. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- In seven multi-centre clinical trials of up to 2 years duration, no clinically relevant changes in blood pressure were observed with ZOELY.
- The following conditions have been reported to occur or deteriorate with oestrogen-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 oestrogens 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.
- There is no evidence for a need to alter the therapeutic regimen in diabetics using ZOELY.
- 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 contraindication (see 4.3 and 4.4). 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 4.2), gastrointestinal disturbances during active tablet taking (see 4.2), or use of concomitant medication that decrease the plasma concentrations of nomegestrol acetate (see 4.5).

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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.

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 medicinal products 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, specifically 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 (e.g. phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John's wort and some HIV protease (e.g. ritonavir and nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine and efavirenz.

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.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. ritonavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with Hepatitis C virus (HCV) medicines (e.g., boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including nomegestrol acetate~~,~~ or oestrogen. The net effect of these changes may be clinically relevant in some cases.

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 medicinal product, 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 medicinal products, 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, dilitazem, erythromycin) CYP3A inhibitors may increase the serum concentrations of oestrogens or progestins.

Interaction studies were not performed with ZOELY, but 2 studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed NOMAC-E2 combination (NOMAC 3,75 mg + 1,5 mg E2) in post-menopausal women.

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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 rifamycin's such as rifampicin, rifabutin and rifampentine 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).

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 medications containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens. 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 4.3).

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

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.

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

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.

Tabulated summary 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		Disturbance in attention
Eye disorders				Dry eye, contact lens intolerance
Vascular disorders			Hot flushes	
Gastrointestinal disorders		Nausea	Abdominal distension	Dry mouth
Skin and subcutaneous tissue disorders	Acne[2]		Hyperhydrosis, 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	Hypomenorrhoea, breast swelling, galactorrhoea, uterine spasm, premenstrual	Vaginal odour, vulvovaginal discomfort

			syndrome, breast mass, dyspareunia, vulvovaginal dryness	
General disorders and administrative site conditions			Irritability, oedema	Hunger
Investigations		Increased weight	Increased hepatic enzyme	

[1] The most appropriate MedDRA term (version 13.1) 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.

Vascular disorders and immune system disorders
In addition to the above-mentioned adverse reactions, venous thromboembolism, arterial thromboembolism and 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 oestrogen 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 4.8). There are no antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.18.8 Ovulation controlling agents

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 oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

17β-estradiol, is a natural oestrogen 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 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. Oestrogens 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 sulfateses. 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 oestrogen 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

No data on efficacy and safety are available in adolescents below 18 years.

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 oestrogenic and gestagen effects.

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

Genotoxity 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

Lactose monohydrate, microcrystalline cellulose, crospovidone, talc, magnesium stearate, colloidal silica anhydrous.

White active tablets:

Tablet coating: Polyvinyl alcohol, titanium dioxide, macrogol, talc.

Yellow placebo tablets:

Tablet coating: Polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide yellow and iron oxide black.

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.

Film-coated tablet.

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

Date of Approval: 21 July 2022

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

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

21 July 2022