

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zoely 2.5 mg/1.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white active tablet contains 2.5 mg norgestrel acetate and 1.5 mg estradiol (as hemihydrate).
Each yellow placebo tablet does not contain active substances.

Excipients with known effect

Each white active tablet contains 57.7 mg of lactose monohydrate.
Each yellow placebo tablet contains 61.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

The active tablet is white, round and coded 'ne' on both sides.
The placebo tablet is yellow, round and coded 'p' on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral contraception.

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).

4.2 Posology and method of administration

Posology

One tablet is to be taken daily for 28 consecutive days. Each pack starts with 24 white active tablets, followed by 4 yellow placebo tablets. 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 2-3 after intake of the last white tablet and may not have finished before the next pack is started. See 'Cycle control' in section 4.4.

Special populations

Renal impairment

Although data in renal impaired patients are not available, renal impairment is unlikely to affect the elimination of norgestrel acetate and estradiol.

Hepatic impairment

No clinical studies have been performed in patients with hepatic insufficiency. Since the metabolism of steroid hormones might be impaired in patients with severe hepatic disease, the use of Zoely in

these women is not indicated as long as liver function values have not returned to normal (see section 4.3).

Paediatric population

Safety and efficacy have not been established in adolescents under 18 years of age. There is no relevant use of Zoely in children and pre-menarchal adolescents.

Method of administration

Oral use.

How to take Zoely

Tablets must be taken every day at about the same time without regard to meals. Tablets should be taken with some liquid as needed, and in the order as directed on the blister. Stickers marked with the 7 days of the week are provided. The woman should choose the sticker that starts with the day she begins taking the tablets and stick it on the blister.

How to start Zoely

No preceding hormonal contraceptive use (in the past month)

Tablet-taking has to start on day 1 of the woman's menstrual cycle (i.e. the first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary.

Changing from a CHC (combined oral contraceptive (COC), vaginal ring or transdermal patch)

The woman should start with Zoely preferably on the day after the last active tablet-taking (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Zoely preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestogen-only-method (minipill, implant, injectable) or from a hormone-medicated intra uterine system (IUS)

The woman may switch any day from the minipill and Zoely should be started on the next day. An implant or IUS may be removed 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 table-taking.

Following first-trimester abortion

The woman may start the tablet-taking immediately. When doing so, no additional contraceptive measures are necessary.

Following delivery or second-trimester abortion

The woman should be advised to start the tablet-taking 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 until she has completed 7 days of uninterrupted white active tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

For breast-feeding women see section 4.6.

Management of missed tablets

The following advice only refers to missed white active tablets:

If the woman 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 further tablets at the usual time.

If the woman 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.

Day 1-7

The woman should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used 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 8-17

The woman should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions until she has completed 7 days of uninterrupted white tablet-taking.

Day 18-24

The risk of reduced reliability is imminent because of the forthcoming yellow placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The woman should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until 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 woman is unlikely to have a withdrawal bleeding until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue 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 white active tablets is not more than 4, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleeding in the placebo tablet phase, the possibility of a pregnancy should be considered.

Please note: If the woman is not sure about the number or colour of tablets missed and what advice to follow, a barrier method should be used until she has completed 7 days of uninterrupted white active tablet-taking.

The following advice only refers to missed yellow placebo tablets:

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 gastro-intestinal disturbances

In case of severe gastro-intestinal disturbance (e.g., vomiting or diarrhoea), absorption of the active substances may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 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 in section 4.2 "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 placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the white active tablets in the second pack. Regular intake of Zoely is then resumed after the yellow placebo tablets have been taken of the second pack. During the extension the woman may experience breakthrough-bleeding or spotting.

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

4.3 Contraindications

CHCs must not be used in the following conditions. Should any of the conditions appear for the first time during Zoely use, the medicinal product should be stopped immediately.

- 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) or 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.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

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 doctor to determine whether the use of Zoely should be discontinued. All data presented below are based upon epidemiological data obtained with CHCs containing ethinylestradiol and apply to Zoely.

Risk of venous thromboembolism (VTE)

- The use of any combined hormonal contraceptive (CHC) increases the 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 6¹ will develop a VTE in one year.
- The number of VTEs per year with low dose CHCs is fewer than the number expected in women during pregnancy or in the postpartum period.
- VTE may be fatal in 1-2 % of cases.
- Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal, or retinal veins and arteries.

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

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).

¹ Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m ²)	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.
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 pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on "Pregnancy and lactation" 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.

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

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

- An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). No epidemiological data on the risk of cervical cancer in users of Zoely are available.
- With the use of the higher-dosed COCs (50 micrograms ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to 17 β -estradiol-containing COCs remains to be confirmed.
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. 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.
- 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. 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, 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.

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

Hepatitis C

- During clinical trials with the hepatitis C virus (HCV) combination 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 medicinal products 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 medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug 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.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC, then it is prudent for the physician to 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 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.
- Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, 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 occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.
- Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). 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.

Medical examination/consultation

Prior to the initiation or reinstatement 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 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 user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against human immunodeficiency virus (HIV) infections (which can cause acquired immunodeficiency syndrome [AIDS]) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g., missed tablets (see section 4.2), gastro-intestinal disturbances during active tablet-taking (see section 4.2) or use of concomitant medicinal products that decrease the plasma concentrations of nomegestrol acetate and/or estradiol (see section 4.5).

Cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about 3 cycles. The percentage of women using Zoely experiencing intracyclic bleeding after this adaptation period ranged from 15-20 %.

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 the withdrawal bleeding in women using Zoely is on average 3-4 days. Users of Zoely may also miss their withdrawal bleeding although not being pregnant. During clinical trials, absence of withdrawal bleeding ranged over the cycles 1-12 from 18 % to 32 %. In such cases, absence of withdrawal bleeding was not associated with a higher occurrence of breakthrough bleeding/spotting in the subsequent cycles. 4.6 % of the women did not have a withdrawal bleeding in the first three cycles of use and the occurrences of absence of withdrawal bleeding in the later cycles of use were high in this subgroup, ranging from 76 % to 87 % of women. 28 % of the women experienced absence of withdrawal bleeding in at least one of the cycles 2, 3 and 4, associated with higher occurrences of absence of withdrawal bleeding in the later cycles of use, ranging from 51 % to 62 %.

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. However, pregnancy must be ruled out before Zoely use is continued, if Zoely has not been taken as directed or if two consecutive withdrawal bleedings are missed.

Paediatric population

It is unknown whether the amount of estradiol in Zoely is sufficient to maintain adequate levels of estradiol in adolescents, especially for bone mass accrual (see section 5.2).

Laboratory tests

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

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions

Note: The prescribing information of concomitant medicinal products should be consulted to identify potential interactions.

Influence of other medicinal products on Zoely

Interactions between oral contraceptives and enzyme-inducing medicinal products may lead to breakthrough bleeding and/or contraceptive failure.

Hepatic metabolism: Interactions can occur with substances that induce CYP450 enzymes, resulting in reduced concentrations of sex hormones and decreased effectiveness of combined oral contraceptives, including Zoely. These substances are represented mostly with anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate); anti-infective drugs (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort; bosentan and HIV or Hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz).

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

A barrier contraceptive method should also be used during the concomitant use of an enzyme inducer, and for 28 days after its discontinuation. In case of long-term treatment with hepatic enzyme-inducing substances another method of contraception should be considered.

If concomitant drug 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.

Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestogens.

Medicinal product interaction studies were not performed with Zoely, but two studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed norgestrel acetate-estradiol combination (norgestrel acetate 3.75 mg + 1.5 mg estradiol) in post-menopausal women. Concomitant use of rifampicin decreases the $AUC_{0-\infty}$ of norgestrel acetate by 95 % and increases the $AUC_{0-t_{last}}$ 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 norgestrel acetate were observed, which were of no clinical relevance. Similar conclusions are expected in women of childbearing potential.

Influence of Zoely on other medicinal products

Contraceptives containing ethinylestradiol 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 HCV combination drug 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 medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Zoely is not indicated during pregnancy.

If pregnancy occurs while taking Zoely, further intake should be stopped. Most epidemiological studies have revealed neither an increased risk of birth defects in infants born to women who used ethinylestradiol-containing COCs prior to pregnancy, nor a teratogenic effect when ethinylestradiol-containing COCs were taken inadvertently during early pregnancy.

Clinical data on a limited number of exposed pregnancies indicate no adverse effect of Zoely on the foetus or neonate.

In animal studies, reproductive toxicity has been observed with the norgestrel acetate / estradiol combination (see preclinical safety data in section 5.3).

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

Breast-feeding

Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the breast milk, but there is no evidence that this adversely affects infant health.

Breast-feeding may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should not be recommended until the breast-feeding mother has completely weaned her child and an alternative method of contraception should be proposed to women wishing to breastfeed.

Fertility

Zoely is indicated for the prevention of pregnancy. For information on return to fertility, see section 5.1.

4.7 Effects on ability to drive and use machines

Zoely has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Six multi-centre clinical trials of up to one-year duration were used to evaluate safety of Zoely. In total 3,434 women, aged 18-50, were enrolled and completed 33,828 cycles.

Most commonly reported adverse reactions in these clinical trials were acne (15.4%) and withdrawal bleeding irregular (9.8%).

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 adverse reactions that have been reported in clinical trials or during post-marketing use with Zoely are listed in the table below.

Adverse reactions are listed according to the MedDRA system organ class and ranked under frequency groupings using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1,000$).

Table: List of adverse reactions

System organ class	Adverse reaction in MedDRA Term ¹			
	Very common	Common	Uncommon	Rare
Metabolism and nutrition disorders			increased appetite, fluid retention	decreased appetite
Psychiatric disorders		decreased libido, depression/ depressed mood, mood altered		increased libido

System organ class	Adverse reaction in MedDRA Term ¹			
	Very common	Common	Uncommon	Rare
Nervous system disorders		headache, migraine		cerebrovascular accident, transient ischaemic attack, disturbance in attention
Eye disorders				contact lens intolerance/dry eye
Vascular disorders			hot flush	venous thromboembolism
Gastrointestinal disorders		nausea	abdominal distension	dry mouth
Hepatobiliary disorders				cholelithiasis, cholecystitis
Skin and subcutaneous tissue disorders	acne		hyperhidrosis, alopecia, pruritus, dry skin, seborrhea	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 syndrome, breast mass, dyspareunia, vulvovaginal dryness	vaginal odour, vulvovaginal discomfort
General disorders and administration site conditions			irritability, oedema	hunger
Investigations		weight increased	hepatic enzyme increased	

¹The 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.

In addition to the above-mentioned adverse reactions, hypersensitivity reactions have been reported in Zoely users (frequency unknown).

Description of selected adverse reactions

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, which are discussed in more detail in section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Multiple doses up to five 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. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and estrogens, fixed combinations, ATC code: G03AA14.

Mechanism of action

Nomegestrol acetate is a highly selective progestogen derived from the naturally occurring steroid hormone, progesterone. Nomegestrol acetate has a strong affinity for the human progesterone receptor and has an anti-gonadotropic activity, a progesterone receptor-mediated anti-oestrogenic activity, a moderate anti-androgenic activity, and is devoid of any oestrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The oestrogen contained in Zoely is 17 β -estradiol, an oestrogen identical to the endogenous human 17 β -estradiol.

The contraceptive effect of Zoely is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Clinical efficacy and safety

In two randomised, open-label, comparative efficacy-safety trials, more than 3,200 women have been treated for up to 13 consecutive cycles with Zoely and more than 1,000 women with drospirenone 3 mg – ethinylestradiol 30 μ g (21/7 regimen).

In the Zoely group, acne was reported by 15.4 % of the women (versus 7.9 % in the comparator group), weight increased was reported by 8.6 % of the women (versus 5.7 % in the comparator group), and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding) was reported by 10.5 % of the women (versus 0.5 % in the comparator group).

In the clinical trial performed with Zoely in the European Union the following Pearl Indices for the age class 18-35 years were calculated:

Method failure: 0.40 (upper limit 95 % confidence interval 1.03).

Method and user failure: 0.38 (upper limit 95 % confidence interval 0.97).

In the clinical trial performed with Zoely in the United States the following Pearl Indices for the age class 18-35 years were calculated:

Method failure: 1.22 (upper limit 95 % confidence interval 2.18).

Method and user failure: 1.16 (upper limit 95 % confidence interval 2.08).

In a randomised, open label trial, 32 women were treated for 6 cycles with Zoely.

After discontinuation of Zoely, return to ovulation in the first 28 days after last tablet intake was observed in 79 % of the women.

Endometrial histology was investigated in a subgroup of women (n=32) in one clinical study after 13 cycles of treatment. There were no abnormal results.

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

Absorption

Orally administered nomegestrol acetate is rapidly absorbed.

Maximum plasma concentrations of nomegestrol acetate of about 7 ng/mL are reached at 2 h after single administration. 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 (97-98 %), 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 $1,645 \pm 576$ L.

Biotransformation

Nomegestrol acetate is metabolized into several inactive hydroxylated metabolites by liver cytochrome P450 enzymes, mainly CYP3A4 and CYP3A5 with possible contribution of CYP2C19 and CYP2C8. 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 L/h.

Elimination

The elimination half-life ($t_{1/2}$) is 46 h (ranging from 28-83 h) 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 within 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 0.625-5 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 h after dosing. Average steady state plasma concentrations are 4 ng/mL.

Drug drug interactions

Nomegestrol acetate causes *in vitro* no notable induction or inhibition of any cytochrome P450 enzymes and has no clinically relevant interaction with the P-gp transporter.

Estradiol

Absorption

Estradiol is subject to a substantial first-pass effect after oral administration. The absolute bioavailability is about 1 %. No clinically relevant effect of food was observed on the bioavailability of estradiol.

Distribution

The distribution of exogenous and endogenous 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 1-2 % is unbound.

Biotransformation

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

Elimination

Estradiol is rapidly cleared from the circulation. Due to metabolism and enterohepatic circulation, a large circulating pool of oestrogen sulfates and glucuronides is present. This results in a highly variable baseline-corrected elimination half-life of estradiol, which is calculated to be 3.6 ± 1.5 h, after intravenous administration.

Steady-state conditions

Maximum serum concentrations of estradiol are about 90 pg/mL and are reached 6 h after dosing. Average serum concentrations are 50 pg/mL and these estradiol levels correspond with the early and late phase of a woman's menstrual cycle.

Special populations

Effect of renal impairment

No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of Zoely.

Effect of hepatic impairment

No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Zoely. However, steroid hormones may be poorly metabolized in women with impaired liver function.

Ethnic groups

No formal studies were performed to assess pharmacokinetics in ethnic groups.

Paediatric population

The pharmacokinetics of nomegestrol acetate (primary objective) after single oral dosing of Zoely in healthy postmenarcheal female adolescents and adult subjects were similar. However, after single oral dosing, for the estradiol component (secondary objective), the exposure was 36 % lower in adolescents versus adult subjects. The clinical relevance of this result is unknown.

5.3 Preclinical safety data

Repeated 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.

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 anhydrous silica

Tablet coat (white active film-coated tablets)

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)

Tablet coating (yellow placebo film-coated tablets)

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Yellow iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium blister containing 28 film-coated tablets (24 white active tablets and 4 yellow placebo tablets).

Pack sizes: 28, 84, 168 and 364 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

COC tablets (including Zoely tablets) no longer required should not be disposed via wastewater or the municipal sewage system. The hormonal active compounds in the tablets 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. MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/690/001
EU/1/11/690/002
EU/1/11/690/003
EU/1/11/690/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2011
Date of latest renewal: 10 May 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Delpharm Lille S.A.S.
Parc d'Activités Roubaix-Est
22 Rue de Toufflers
CS 50070
59452 LYS-LEZ-LANNOY
France

Teva Operations Poland Sp. z o.o.
ul. Mogilska 80
31-546 Krakow
Poland

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zoely 2.5 mg/1.5 mg film-coated tablets
nomegestrol acetate/estradiol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each white active tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate).
Each yellow placebo tablet does not contain active substances.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 film-coated tablets
84 film-coated tablets
168 film-coated tablets
364 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/690/001 28 film-coated tablets
EU/1/11/690/002 84 film-coated tablets
EU/1/11/690/003 168 film-coated tablets
EU/1/11/690/004 364 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zoely

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zoely 2.5 mg/1.5 mg tablets
nomegestrol acetate/estradiol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

[Box for placing day label stating:] Place day label here
[Day numbering for each individual tablet:] Start,2,28
[Arrows indicating the sequence of the tablets:] →

DAY LABEL SHEET INCLUDING STICKERS PROVIDED WITH THE LEAFLET

Day label sheet

Choose the day label that begins with your starting day.

Place the label on the blister over the words 'Place day label here'.

SUN MON TUE WED THU FRI SAT
MON TUE WED THU FRI SAT SUN
TUE WED THU FRI SAT SUN MON
WED THU FRI SAT SUN MON TUE
THU FRI SAT SUN MON TUE WED
FRI SAT SUN MON TUE WED THU
SAT SUN MON TUE WED THU FRI

[Second day label sheet for box of 3 blisters stating, twice:]

SUN MON TUE WED THU FRI SAT
MON TUE WED THU FRI SAT SUN
TUE WED THU FRI SAT SUN MON
WED THU FRI SAT SUN MON TUE
THU FRI SAT SUN MON TUE WED
FRI SAT SUN MON TUE WED THU
SAT SUN MON TUE WED THU FRI

[In front of day labels intended for second blister:] Blister 2

[In front of day labels intended for third blister:] Blister 3

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zoely 2.5 mg/1.5 mg film-coated tablets norgestrol acetate/estradiol

Important things to know about combined hormonal contraceptives (CHCs):

- They are one of the most reliable reversible methods of contraception if used correctly.
- They slightly increase the risk of having a blood clot in the veins and arteries, especially in the first year or when restarting a combined hormonal contraceptive following a break of 4 or more weeks.
- Please be alert and see your doctor if you think you may have symptoms of a blood clot (see section 2 “Blood clots”).

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zoely is and what it is used for
2. What you need to know before you use Zoely
3. How to use Zoely
4. Possible side effects
5. How to store Zoely
6. Contents of the pack and other information

1. What Zoely is and what it is used for

Zoely is a contraceptive pill that is used to prevent pregnancy.

- All 24 white film-coated tablets are active tablets that contain a small amount of two different female hormones. These are norgestrol acetate (a progestogen) and estradiol (an oestrogen).
- The 4 yellow film-coated tablets are inactive tablets that do not contain hormones and are called placebo tablets.
- Contraceptive pills that contain two different hormones, like Zoely, are called ‘combined pills’.
-
- Norgestrol acetate (the progestogen in Zoely) and estradiol (the oestrogen in Zoely) work together to prevent ovulation (release of an egg from the ovary) and to reduce the chance of any released egg being fertilised and making you pregnant.

2. What you need to know before you use Zoely

General notes

Before you start using Zoely you should read the information on blood clots (thrombosis) in section 2. It is particularly important to read the symptoms of a blood clot – see section 2 “Blood clots”.

Before you can begin taking Zoely, your doctor will ask you about your personal health history and that of your close relatives in order to give you an individual advice on the treatment. The doctor will

also measure your blood pressure and, depending upon your personal situation, may also carry out some other tests.

This leaflet describes situations where you should stop taking the pill, or where the pill protection against pregnancy may be decreased. In such situations you should not have sex or you should take extra non-hormonal contraceptive precautions, e.g., use a condom or another barrier method. Do not use rhythm or temperature methods. These methods may not protect against pregnancy because the pill alters the usual changes in temperature and cervical mucus that occur during the menstrual cycle.

Zoely, like other hormonal contraceptives, does not protect against human immunodeficiency virus (HIV) infection (which can cause acquired immunodeficiency syndrome, AIDS) or any other sexually transmitted disease.

Do not use Zoely

You must not use Zoely if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.

- if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolism, PE) or other organs;
- if you have a disorder affecting your blood clotting - for instance, protein C deficiency, protein S deficiency, antithrombin – III deficiency, Factor V Leiden or antiphospholipid antibodies;
- if you need an operation or if you are off your feet for a long time (see section ‘Blood clots’);
- if you have ever had a heart attack or a stroke;
- if you have ever had angina pectoris (a condition that causes severe chest pain and may be a first sign of blocked blood vessels around your heart, known as heart attack) or transient ischaemic attack (TIA, temporary stroke symptoms);
- if you have any of the following diseases that may increase your risk of a clot in the arteries:
 - severe diabetes with blood vessel damage;
 - very high blood pressure;
 - a very high level of certain fat in the blood (cholesterol or triglycerides);
 - a condition known as hyperhomocysteinaemia;
- if you have ever had a type of migraine called ‘migraine with aura’;
- if you have ever had inflammation of the pancreas (pancreatitis) associated with high levels of fat in your blood;
- if you have ever had a severe liver disease and your liver function is not yet working normally;
- if you have ever had a benign or malignant tumour in the liver;
- if you have ever had, or if you may have, cancer of the breast or the genital organs;
- if you have meningioma or have ever been diagnosed with a meningioma (a generally benign tumour of the tissue layer between the brain and the skull).
- if you have any unexplained bleeding from the vagina;
- if you are allergic to estradiol or norgestrel acetate, or any of the other ingredients of this medicine (listed in section 6).

If any of these conditions appear for the first time while using Zoely, stop taking it at once and tell your doctor. In the meantime, use a non-hormonal contraceptive. See also ‘General Notes’ in section 2 above.

Warnings and precautions

Talk to your doctor or pharmacist before using Zoely.

When should you contact your doctor?

Seek urgent medical attention if you:

- notice possible signs of a blood clot that may mean you are suffering from a blood clot in the leg (i.e., deep vein thrombosis), a blood clot in the lung (i.e., pulmonary embolism), a heart attack or a stroke (see “Blood clots” section below).

For a description of the symptoms of these serious side effects please go to “How to recognise a blood clot”.

- notice any changes in your own health, especially involving any of the items mentioned in this leaflet (see also in section 2 ‘Do not use Zoely’; do not forget about the changes in the health of your immediate family);
- feel a lump in your breast;
- experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives together with difficulty breathing;
- are going to use other medicines (see also in section 2 ‘Other medicines and Zoely’);
- are to be immobilised or are to have surgery (tell your doctor at least four weeks in advance);
- have unusual, heavy vaginal bleeding;
- forgot one or more tablets in the first week of the blister pack and had unprotected sex in the seven days before (see also in section 3 ‘If you forget to take Zoely’);
- have severe diarrhoea or experience severe vomiting;
- miss periods and suspect you may be pregnant (do not start the next blister pack until your doctor tells you, see also in section 3 ‘If you have missed one or more periods’).

Tell your doctor if any of the following conditions apply to you.

If the condition develops, or gets worse while you are using Zoely, you should also tell your doctor if you have:

- hereditary and acquired angioedema. Consult your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing. Medicines containing oestrogens may induce or worsen symptoms of angioedema;
- epilepsy (see in section 2 ‘Other medicines and Zoely’);
- liver disease (for instance jaundice) or gallbladder disease (for instance gallstones);
- diabetes;
- depression;
- Crohn’s disease or ulcerative colitis (chronic inflammatory bowel disease);
- systemic lupus erythematosus (SLE, a disease affecting your natural defence system);
- haemolytic uraemic syndrome (HUS, a disorder of blood clotting causing failure of the kidneys);
- sickle cell anaemia (an inherited disease of the red blood cells);
- elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);
- an inflammation in the veins under the skin (superficial thrombophlebitis);
- varicose veins.
- a condition that occurred for the first time or worsened during pregnancy or previous use of female hormones (e.g. hearing loss, porphyria [a disease of the blood], herpes gestationis [skin rash with vesicles during pregnancy], Sydenham’s chorea [a disease of the nerves in which sudden movements of the body occur]);
- or have ever had chloasma (a skin yellowish-brown pigment patches, so called ‘pregnancy patches’, particularly on the face). If so, avoid too much exposure to the sun or ultraviolet light;

Also tell your doctor if:

- a close relative has or has ever had breast cancer;
- you need an operation or if you are off your feet for a long time (see in section 2 'Blood clots');
- you have just given birth you are at an increased risk of blood clots. You should ask your doctor how soon after delivery you can start taking Zoely.

BLOOD CLOTS

Using a combined hormonal contraceptive such as Zoely increases your risk of developing a blood clot compared with not using one. In rare cases a blood clot can block blood vessels and cause serious problems.

Blood clots can develop

- in veins (referred to as 'venous thrombosis', 'venous thromboembolism' or VTE)
- in the arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.

It is important to remember that the overall risk of a harmful blood clot due to Zoely is small.

HOW TO RECOGNISE A BLOOD CLOT

Seek urgent medical attention if you notice any of the following signs or symptoms.

Are you experiencing any of these signs?	What are you possibly suffering from?
<ul style="list-style-type: none"> • swelling of one leg or along a vein in the leg or foot especially when accompanied by: <ul style="list-style-type: none"> • pain or tenderness in the leg which may be felt only when standing or walking • increased warmth in the affected leg • change in colour of the skin on the leg e.g. turning pale, red or blue 	Deep vein thrombosis
<ul style="list-style-type: none"> • sudden unexplained breathlessness or rapid breathing; • sudden cough without an obvious cause, which may bring up blood; • sharp chest pain which may increase with deep breathing; • severe light headedness or dizziness; • rapid or irregular heartbeat; • severe pain in your stomach; <p>If you are unsure, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g., a ‘common cold’).</p>	Pulmonary embolism
<p>Symptoms most commonly occur in one eye:</p> <ul style="list-style-type: none"> • immediate loss of vision or • painless blurring of vision which can progress to loss of vision 	Retinal vein thrombosis (blood clot in the eye)
<ul style="list-style-type: none"> • chest pain, discomfort, pressure, heaviness • sensation of squeezing or fullness in the chest, arm or below the breastbone; • fullness, indigestion or choking feeling; • upper body discomfort radiating to the back, jaw, throat, arm and stomach; • sweating, nausea, vomiting or dizziness; • extreme weakness, anxiety, or shortness of breath; • rapid or irregular heartbeats 	Heart attack
<ul style="list-style-type: none"> • sudden weakness or numbness of the face, arm or leg, especially on one side of the body; • sudden confusion, trouble speaking or understanding; • sudden trouble seeing in one or both eyes; • sudden trouble walking, dizziness, loss of balance or coordination; • sudden, severe or prolonged headache with no known cause; • loss of consciousness or fainting with or without seizure. <p>Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.</p>	Stroke
<ul style="list-style-type: none"> • swelling and slight blue discolouration of an extremity; • severe pain in your stomach (acute abdomen). 	Blood clots blocking other blood vessels

BLOOD CLOTS IN A VEIN

What can happen if a blood clot forms in a vein?

- The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.
- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?

The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more.

After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.

When you stop Zoely your risk of a blood clot returns to normal within a few weeks.

What is the risk of developing a blood clot?

The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are taking.

The overall risk of a blood clot in the leg or lung (DVT or PE) with Zoely is small.

- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate, about 5-7 will develop a blood clot in a year.
- The risk of a blood clot with Zoely compares to the risk with a combined hormonal contraceptive that contains levonorgestrel.
- The risk of having a blood clot will vary according to your personal medical history (see “Factors that increase your risk of a blood clot” below).

	Risk of developing a blood clot in a year
Women who are not using a combined hormonal pill and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive pill containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using Zoely	About the same as with other combined hormonal contraceptives including contraceptives containing levonorgestrel

Factors that increase your risk of a blood clot in a vein

The risk of a blood clot with Zoely is small but some conditions will increase the risk. Your risk is higher:

- if you are very overweight (body mass index or BMI over 30 kg/m²);
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g., below the age of about 50 years). In this case you could have a hereditary blood clotting disorder;

- if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of Zoely may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop Zoely ask your doctor when you can start using it again.
- as you get older (particularly above about 35 years);
- if you gave birth less than a few weeks ago.

The risk of developing a blood clot increases the more conditions you have.

Air travel (for longer than 4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.

It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that Zoely needs to be stopped.

If any of the above conditions change while you are using Zoely, for example a close family member has a thrombosis for no known reason or you gain a lot of weight, tell your doctor.

BLOOD CLOTS IN AN ARTERY

What can happen if a blood clot forms in an artery?

Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery

It is important to note that the risk of a heart attack or stroke from using Zoely is very small but can increase:

- with increasing age (beyond about 35 years);
- **if you smoke.** When using a combined hormonal contraceptive like Zoely you are advised to stop smoking. If you are unable to stop smoking and are older than 35 years your doctor may advise you to use a different type of contraceptive;
- if you are overweight;
- if you have high blood pressure;
- if a member of your immediate family has had a heart attack or stroke at a young age (less than about 50 years). In this case you could also have a higher risk of having a heart attack or stroke;
- if you, or someone in your immediate family, have a high level of fat in the blood (cholesterol or triglycerides);
- if you get migraines, especially migraines with aura;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation)
- if you have diabetes.

If you have more than one of these conditions or if any of them are particularly severe, the risk of developing a blood clot may be increased even more.

If any of the above conditions change while you are using Zoely, for example, you start smoking, a close family member experiences a thrombosis for no known reason or you gain a lot of weight, tell your doctor.

Cancer

Breast cancer has been detected slightly more often in women using combined contraceptives, but it is not known if it is caused by the combined pills. For example, it may be that tumours are detected more in women on combined pills because they have breast examination by their doctor more often. After stopping the combined pill, the increased risk gradually reduces.

It is important to check your breasts regularly and you should contact your doctor if you feel any lump. You should also tell your doctor if a close relative has, or ever had breast cancer (see section 2 “Warnings and precautions”).

In rare cases, benign (noncancerous) liver tumours, and in even rarer cases malignant (cancerous) liver tumours have occurred in pill users. Contact your doctor if you have unusual severe abdominal pain.

Cervical cancer is caused by an infection with the human papilloma virus (HPV). It has been reported to occur more often in women using the pill for more than 5 years. It is not known if this is due to the use of hormonal contraceptives or to other factors, such as difference in sexual behaviour.

Meningiomas

Use of norgestrel acetate has been linked to the development of a generally benign tumours of the tissue layer between the brain and the skull (meningioma). The risk increases especially when you use it at high doses for longer duration (several years). If you are diagnosed with meningioma, your doctor will stop your treatment with Zoely (see section 'Do not use Zoely'). If you notice any symptoms such as changes in vision (e.g. seeing double or blurriness), hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures, weakness in your arms or legs, you must tell your doctor straightaway.

Psychiatric disorders

Some women using hormonal contraceptives including Zoely have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

Laboratory tests

If you are having any blood or urinary test, tell your doctor that you are using Zoely as it may affect the results of some tests.

Children and adolescents

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

Other medicines and Zoely

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Also tell any other healthcare professional who prescribes or dispenses another medicine that you use Zoely.

- There are medicines that can make Zoely less effective in preventing pregnancy, or can cause unexpected bleeding. These include medicines used to treat:
 - epilepsy (e.g. primidone, phenytoin, phenobarbital, carbamazepine, oxcarbazepine, topiramate, felbamate);
 - tuberculosis (e.g. rifampicin);
 - HIV infection (e.g. rifabutin, ritonavir, efavirenz);
 - Hepatitis C virus (HCV) infection (e.g. protease inhibitors);
 - other infectious diseases (e.g. griseofulvin);
 - high blood pressure in the blood vessels in the lungs, known as pulmonary arterial hypertension (bosentan).
- The herbal product St. John's wort (*Hypericum perforatum*) may also stop Zoely from working properly. If you want to use herbal products containing St. John's wort while you are already using Zoely you should check with your doctor first.
- If you are taking medicines or herbal products that might make Zoely less effective, a barrier contraceptive method should also be used. Since the effect of another medicine on Zoely may last up to 28 days after you stop the medicine, it is necessary to use the additional barrier contraceptive method for that long.
- Some medicines can increase the levels of the active substances of Zoely in the blood. The effectiveness of the pill is maintained, but tell your doctor if you are using anti-fungal medicines containing ketoconazole.
- Zoely may also interfere with the working of other medicines, such as the anti-epileptic lamotrigine.

- The Hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4) may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Zoely contains estradiol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Zoely with this HCV combination regimen. Your doctor will advise you.

Pregnancy and breast-feeding

Zoely must not be used by women who are pregnant, or who think they may be pregnant. If you get pregnant while using Zoely you should stop using Zoely immediately and contact your doctor. If you want to stop Zoely because you want to get pregnant, see in section 3 'If you stop taking Zoely'.

Zoely is not usually recommended for use during breast-feeding. If you wish to use the pill while breast-feeding, you should check with your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Zoely has no or negligible effect on your ability to drive and use machines.

Zoely contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use Zoely

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

When and how to take the tablets

The Zoely blister contains 28 film-coated tablets: 24 white tablets with the active substances (number 1-24) and 4 yellow tablets without active substances (number 25-28).

Each time you start a new blister of Zoely, take the number 1 white active tablet in the left-hand top corner (see 'Start'). Choose from the 7 stickers with day indicators the one in the grey column that begins with your starting day. For example, if you start on a Wednesday, use the day label sticker that starts with 'WED'. Place it on the blister, just above the row of white active tablets where it reads 'Place day label here'. This allows you to check whether you took your daily tablet.

Take one tablet each day at about the same time, with some water if necessary.

Follow the direction of the arrows on the blister, so use the white active tablets first and then the yellow placebo tablets.

Your period will start during the 4 days that you use the yellow placebo tablets (so-called withdrawal bleeding). Usually it will start 2-3 days after you use the last white active tablet and may not have finished before you start the next blister.

Start taking the next blister immediately after you use the last yellow placebo tablet, even if your period hasn't finished. This means that you will always start a new blister on the same day of the week, and also that you have your period on roughly the same days each month.

Some women may not have their period every month when they are using the yellow placebo tablets. If you have taken Zoely every day according to these directions, it is unlikely that you are pregnant (see also section 3 'If you have missed one or more periods').

Starting your first pack of Zoely

If you have not used a contraceptive with hormones in the previous month

Begin with Zoely on the first day of the cycle (that is the first day of your period). If you start Zoely on the first day of your period you are immediately protected against pregnancy. You do not need to use an additional contraceptive method.

Changing from another combined hormonal contraceptive (combined pill, vaginal ring, or transdermal patch)

You can start Zoely preferably on the day after you have taken the last active tablet (the last tablet containing the active substances) of your present pill blister (this means no tablet-free break). If your present pill blister also contains inactive (placebo) tablets you can start Zoely on the day after taking the last **active** tablet (if you are not sure which this is, ask your doctor or pharmacist). You can also start Zoely later, but never later than the day following the tablet-free break of your present pill (or the day after the last inactive tablet of your present pill). In case you change from a vaginal ring or transdermal patch, it is best to start Zoely on the day you remove the ring or patch. You can also start, at the latest, on the day you would have started using the next ring or patch.

If you follow these instructions, it is not necessary to use an additional contraceptive method. If you have any concerns about whether you are protected please seek the advice of your doctor.

Changing from a progestogen-only pill (minipill)

You can switch any day from the progestogen-only pill to start Zoely on the next day, but you must use a barrier method of contraception (for example, a condom) during the first 7 days that you are taking Zoely.

When changing from a progestogen-only injectable, implant or a hormone-medicated intrauterine system (IUS)

Start using Zoely when your next injection is due or on the day that your implant or IUS is removed. But if you are having intercourse, make sure you also use a barrier method of contraception for the first 7 days that you are taking Zoely.

After having a baby

You can start Zoely between 21 and 28 days after having a baby. If you start later than day 28, you must use a barrier method of contraception (for example, a condom) during the first 7 days that you are taking Zoely. If, after having a baby, you have had sex before starting Zoely, you must first be sure that you are not pregnant or you must wait until your next period.

If you are breast-feeding and want to start Zoely after having a baby, see section 2 'Pregnancy and Breast-feeding'.

Ask your doctor or pharmacist what to do if you are not sure when to start.

After a miscarriage or an abortion

Follow the advice of your doctor.

If you take more Zoely than you should

There have been no reports of serious harm from taking too many Zoely tablets. If you have taken several tablets at once, then you may feel sick (nausea), vomit or bleed from the vagina. If you have taken too many Zoely tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice.

If you forget to take Zoely

The following advice only refers to missed **white active** tablets.

- if you are **less than 24 hours late** taking a tablet, the pill protection against pregnancy is maintained. Take the tablet as soon as possible and then take the next tablets at the usual time.
- if you are **24 or more hours late** taking a tablet, the pill protection against pregnancy may be reduced. The more tablets you have forgotten, the higher your risk of becoming pregnant. There is a particularly high risk of becoming pregnant if you miss **white** active tablets at the beginning or at the end of the blister. Therefore you should follow the rules given below.

Day 1-7 of white active tablet intake (see picture and schedule)

Take the forgotten white active tablet as soon as possible, even if this means that you have to take two tablets at the same time, and continue to take the next tablet at the usual time. However, use a barrier method of contraception (for example, a condom) as an extra precaution until you have taken your tablets correctly for 7 days in a row.

If you had sex in the week before missing the tablets, there is a possibility of you becoming or being pregnant. In that case, contact your doctor immediately.

Day 8-17 of white active tablet intake (see picture and schedule)

Take the last missed tablet as soon as you remember (even if this means taking two tablets at the same time) and take the next tablets at the usual time. If you have taken your tablets correctly in the 7 days prior to the missed tablet, the protection against pregnancy is not reduced, and you do not need to use extra precautions. However, if you have missed more than 1 tablet, use a barrier method such as a condom as an extra precaution until you have taken your tablets correctly for 7 days in a row.

Day 18-24 of white active tablet intake (see picture and schedule)

There is a particularly high risk of you becoming pregnant if you miss white active tablets close to the yellow placebo tablet interval. By adjusting your intake schedule this higher risk can be prevented.

The following two options can be followed. You do not need to use extra precautions if you have taken your tablets correctly in the 7 days prior to the missed tablet. If this is not the case, you should follow the first of these two options and use a barrier method of contraception (for example, a condom) as an extra precaution until you have taken your tablets correctly for 7 days in a row.

Option 1: Take the last missed white active tablet as soon as possible, even if this means that you have to take two tablets at the same time, and continue to take the next tablets at the usual time. Start the next blister as soon as the white active tablets in the current blister are finished, so **skip the yellow placebo tablets**. You may not have your period until you take the yellow placebo tablets at the end of the second blister, but you may have light or menstruation-like bleeding while taking the white active tablets.

Option 2: Stop taking the white active tablets and start taking the yellow placebo tablets for a maximum of 3 days so that the total number of placebo plus missed white active tablets is not more than 4. At the end of the yellow placebo tablets intake, start the next blister.

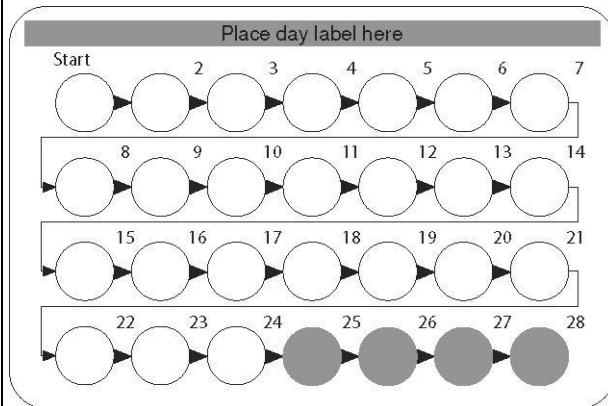
If you cannot remember how many white active tablets you have missed, follow the first option, use a barrier method such as a condom as an extra precaution until you have taken your tablets correctly for 7 days in a row, and contact your doctor (as you may not have been protected from being pregnant).

If you have forgotten to take white active tablets in a blister, and you do not have the expected monthly period while taking the yellow placebo tablets from the same blister, you may be pregnant. You must contact your doctor before you start with the next blister.

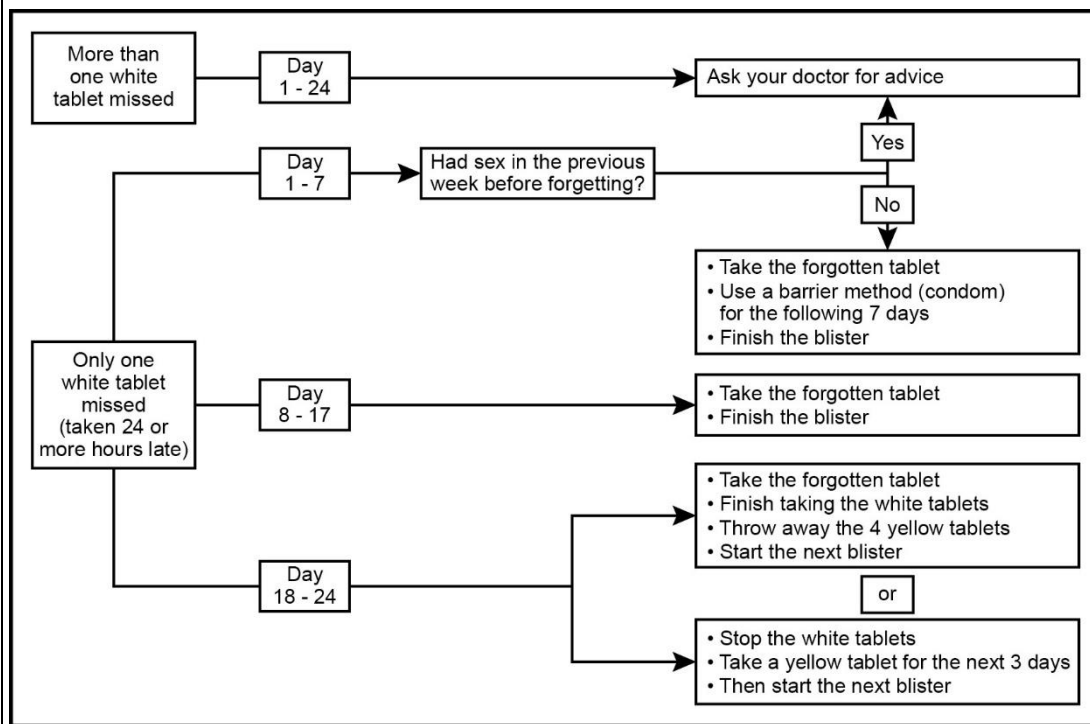
The following advice only refers to forgotten yellow placebo tablets

The last 4 yellow tablets of the fourth row are placebo tablets which do not contain active substances. If you forgot to take one of these tablets, the Zoely protection against pregnancy is maintained. Throw away the yellow placebo tablet(s) you missed and start taking the tablets of the next blister at the usual time.

Picture



Schedule if you are 24 or more hours late taking white active tablets



If you vomit or have severe diarrhoea

If you vomit within 3-4 hours of taking a white active tablet, or you have severe diarrhoea, there is a risk that the active substance in Zoely tablets may not have been completely absorbed into your body. The situation is similar to if you forget a white active tablet. After vomiting or diarrhoea, you must take another white active tablet from a reserve blister as soon as possible. If possible, take it *within 24 hours* of when you normally take your pill. Take the next tablet at the usual time. If this is not possible or 24 or more hours have passed, you should follow the advice given under "If you forget to take Zoely". If you have severe diarrhoea, please tell your doctor.

The yellow tablets are placebo tablets which do not contain active substances. If you vomit or have severe diarrhoea within 3-4 hours of taking a yellow placebo tablet, the Zoely protection against pregnancy is maintained.

If you want to delay your period

Even if it is not recommended, you can delay your period by missing out taking the yellow placebo tablets from the fourth row and going straight to a new blister of Zoely. You may have light or menstruation-like bleeding while using this second blister. When you wish your period to begin during the second blister, stop taking the white active tablets and start taking the yellow placebo tablets.

Finish this second blister by taking the 4 yellow placebo tablets, and then start with the next (third) blister. **If you are not sure what to do, ask your doctor or pharmacist for advice.**

If you want to change the starting day of your period

If you take the tablets according to the instructions, then your period will begin during the placebo days. If you have to change this day, reduce the number of placebo days – when you take the yellow placebo tablets – but never increase them (4 is the maximum). For example, if you start taking the yellow placebo tablets on Friday, and you want to change this to a Tuesday (3 days earlier) you must start a new blister 3 days earlier than usual. You may not have any bleeding during the shortened period of yellow placebo tablet intake. While using the next blister you may have light or menstruation-like bleeding on white active tablet-taking days. **If you are not sure what to do, ask your doctor or pharmacist for advice.**

If you have unexpected bleeding

With all combined pills, for the first few months, you can have some irregular vaginal bleeding (spotting or breakthrough bleeding) between your periods. You may need to use sanitary protection, but keep taking your tablets as usual. Irregular vaginal bleeding usually stops once your body has adjusted to the pill (usually after about 3 months). If bleeding continues, becomes heavy or starts again, contact your doctor.

If you have missed one or more periods

Clinical trials with Zoely have shown that you may occasionally miss your regular monthly period after Day 24.

- If you have taken all the tablets correctly, and you have not vomited or had severe diarrhoea, or used other medicines, then it is very unlikely that you are pregnant. Keep taking Zoely as usual. See also in section 3 ‘If you vomit or have severe diarrhoea’ or in section 2 ‘Other medicines and Zoely’.
- If you have **not** taken all the tablets correctly, or if your expected period does not happen twice in a row, you may be pregnant. Contact your doctor immediately. Do not start the next blister of Zoely until your doctor has checked that you are not pregnant.

If you stop taking Zoely

You can stop taking Zoely at any time. If you do not want to become pregnant, first ask your doctor about other methods of birth control.

If you stop taking Zoely because you want to get pregnant, it is best to wait until you have had a natural period before trying to become pregnant. This will help you to determine when the baby will be due.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any side effect, particularly if severe or persistent, or have any change to your health that you think may be due to Zoely, please talk to your doctor.

An increased risk of blood clots in your veins (venous thromboembolism (VTE)) or blood clots in your arteries (arterial thromboembolism (ATE)) is present for all women taking combined hormonal contraceptives. For more detailed information on the different risks from taking combined hormonal contraceptives, please see section 2, “What you need to know before you use Zoely”.

The following side effects have been linked with the use of Zoely:

Very common (may affect more than 1 in 10 people):

- acne
- changes to menstrual periods (e.g. absence or irregularity)

Common (may affect up to 1 in 10 people):

- decreased interest in sex; depression/depressed mood; mood changes
- headache or migraine
- feeling sick (nausea)
- heavy menstrual periods, breast pain, pelvic pain
- weight gain

Uncommon (may affect up to 1 in 100 people):

- increased appetite, fluid retention (oedema)
- hot flush
- swollen abdomen (belly)
- increased sweating, hair loss, itching, dry skin, oily skin
- heaviness in limbs
- regular but scanty periods, larger breasts, breast lump, milk production while not pregnant, premenstrual syndrome, pain during sex, dryness in the vagina or vulva, spasm of the uterus
- irritability
- increased liver enzymes

Rare (may affect up to 1 in 1,000 people):

- harmful blood clots in a vein or artery, for example:
 - in a leg or foot (i.e., DVT)
 - in a lung (i.e., PE)
 - heart attack
 - stroke
 - mini-stroke or temporary stroke-like symptoms known as a transient ischaemic attack (TIA)
 - blood clots in the liver, stomach/intestine, kidneys or eye.

The chance of having a blood clot may be higher if you have any other conditions that increase this risk. (See section 2 for more information on the conditions that increase risk for blood clots and the symptoms of a blood clot.)

- decreased appetite
- increased interest in sex
- disturbance in attention
- dry eye, contact lens intolerance
- dry mouth
- golden brown pigment patches, mostly in the face, excessive hair growth
- vaginal smell, discomfort in the vagina or vulva
- hunger
- disease of the gallbladder

Allergic (hypersensitive) reactions have been reported in users of Zoely, but the frequency cannot be estimated from the available data.

Further information on the possible side effect changes to menstrual periods (e.g. absence or irregular) during the use of Zoely is described in section 3 ‘When and how to take the tablets’, ‘If you have unexpected bleeding’ and ‘If you have missed one or more periods’).

Reporting of side effects

If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zoely

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Combined pills (including Zoely tablets) no longer required should not be disposed via wastewater or the municipal sewage system. The hormonal active substances in the tablet may have harmful effects if they reach the aquatic environment. Return them to a pharmacy or dispose them in another safe way according to local requirements. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zoely contains

- The active substances are: norgestrel acetate and estradiol
White active film-coated tablets: Each tablet contains 2.5 mg norgestrel acetate and 1.5 mg estradiol (as hemihydrate).
Yellow placebo film-coated tablets: The tablet does not contain active substances.
- The other ingredients are:
Tablet core (white active and yellow placebo film-coated tablets):
Lactose monohydrate (see section 2 'Zoely contains lactose'), microcrystalline cellulose (E460), croscopovidone (E1201), talc (E553b), magnesium stearate (E572) and colloidal anhydrous silica
Tablet coat (white active film-coated tablets):
Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 and talc (E553b)
Tablet coat (yellow placebo film-coated tablets):
Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), yellow iron oxide(E172) and black iron oxide(E172)

What Zoely looks like and contents of the pack

The active film-coated tablets (tablets) are white and round. They are coded 'ne' on both sides. The placebo film-coated tablets are yellow and round. They are coded 'p' on both sides. Zoely comes in blisters of 28 film-coated tablets (24 white active film-coated tablets and 4 yellow placebo film-coated tablets) packed in a ply carton. Pack sizes: 28, 84, 168 and 364 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Theramex Ireland Limited
3rd Floor, Kilmore House,
Park Lane, Spencer Dock,
Dublin 1
D01 YE64
Ireland

Manufacturer

Delpharm Lille S.A.S.
Parc d'Activités Roubaix-Est
22 Rue de Toufflers
CS 50070
59452 LYS-LEZ-LANNOY
France

Teva Operations Poland Sp. z o.o.
ul. Mogilska 80
31-546 Krakow
Poland

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Annex IV
Scientific conclusions

Scientific conclusions

Nomegestrol acetate (NOMAC) and chlormadinone acetate (CMA) are both progestin derivatives with anti-gonadotropic effects. Both progestins have additional antiestrogenic but also antiandrogenic activity. Their antiandrogenic activity has been shown being 30% (CMA) and 90% (NOMAC) compared with cyproterone acetate (CPA) that was set as the reference antiandrogenic progestin with a 100 % antiandrogenic activity in castrated, androgen-treated rats (Kuhl 2005).

Approved indications for nomegestrol acetate and chlormadinone acetate in monotherapy or in combination with estradiol or ethinylestradiol differ between the different strengths and between the different countries. Overall, they are indicated for gynaecological and menstrual disorders, hormone replacement therapy and, at lower doses, as hormonal contraception.

Meningioma is a rare brain tumour which forms from the meninges. Although most meningiomas are benign tumours, their intracranial location may lead to serious and potentially lethal consequences. Women are approximately twice likely to develop it as men, suggesting a role of sexual hormones in the physiopathology.

The risk of meningioma associated with nomegestrol acetate use is known since 2018. Indeed, this risk was then discussed during the PSUSA assessment (PSUSA/00002181/201801) covering nomegestrol monotherapy-containing products and added to the product information (PI). In the meantime, some publications reported case reports of meningioma regression after nomegestrol discontinuation suggesting a hormonal/progestin role of the drug in the growth of these tumours. Additionally, the risk was discussed during the PSUSA assessment of nomegestrol in combination with estradiol (PSUSA/00002182/201801) leading to changes to the PI to recommend close monitoring of meningiomas when used as hormone replacement therapy (HRT). The PI of Zoely was amended to reflect this risk.

For chlormadinone acetate-containing medicinal products, an increase of case reports of meningiomas was observed in France in 2019 and further risk minimisation measures (RMMs) were implemented at national level, including amendments of the PI of all chlormadinone 5 and 10mg containing products to reflect the risk of meningioma.

To further clarify the relationship between both chlormadinone acetate or nomegestrol acetate and the risk of meningioma, two pharmacoepidemiological studies have been conducted by the French group, EPI-PHARE (Nguyen et al. 2021), based on data from SNDS (Système national des données de santé - French National Health Data System). Results suggested an increased risk of meningiomas depending on dose and duration of treatment with nomegestrol acetate or chlormadinone acetate.

On 22 September 2021, the French national competent authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of nomegestrol acetate-containing products and chlormadinone acetate-containing products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 07 July 2022 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The efficacy of chlormadinone acetate or nomegestrol acetate, also in combination with ethinylestradiol or estradiol, in their authorised indications, has been assessed at the time of authorisation in central and national MAA procedures, and is considered to be established.

The two recent cohort studies by Nguyen et al. (2021), aimed to evaluate the real-life impact of prolonged use of CMA or NOMAC on the risk of meningioma in women, add to the current knowledge well-defined, structured, long-term data based on administrative health data from the SNDS (Système National des Données de Santé), which covers around 99% of the French population. The results showed an increased risk for intracranial meningioma after exposure to CMA or NOMAC with high cumulative dose and longer exposure duration, with potential decrease after discontinuation of CMA or NOMAC. The strength of association, the strong dose-dependent effects and the risk reduction observed after treatment discontinuation of at least one year support the association between CMA/NOMAC exposure and increased risk of meningiomas.

The analysis of post-marketing cases points as well towards an increased risk of meningioma during long-term use with high dose products (CMA 5-10 mg and NOMAC 3.75-5 mg) for different indications. For CMA, most cases reported refer to use of the product in the endometriosis indication. For NOMAC, the highest number of cases have been reported in the context of off-label use (contraception and endometriosis) followed by reports in the authorised treatment of uterine leiomyoma and heavy menstrual bleeding.

In addition, a EudraVigilance (EV) analysis of cases of meningioma reported with CMA or NOMAC-containing medicinal products retrieved 359 case reports with CMA-containing products and 461 case reports with NOMAC-containing products, almost all in females, most of them aged between 40 to 60 years. The case reports mainly derived from France with a sharp increase in 2019. Only a few case reports with the low dose NOMAC combination products such as Zoely were retrieved.

Low-dose CMA (1-2 mg)- or low dose NOMAC (2.5 mg)-containing products

The risk of meningioma with the use of CMA or NOMAC has been previously recognised and is currently reflected in the PI as follows:

- Low dose CMA monotherapy-containing products: contraindication in patients with meningioma or history of meningioma.
- Low dose NOMAC combination products: contraindication in patients with meningioma or history of meningioma and a warning on the risk of meningioma.

While, as part of the review, no increased risk specifically in association to the use of low dose products could be identified, it is noted that there are situations where patients may be exposed to low dose products for a long period of time and therefore, the risk of meningioma associated to low dose products is considered a potential important risk. As the risk increases with increasing cumulative dose, PRAC considered that a warning on this risk should be reflected in the PI of low dose CMA (1- 2 mg)- or NOMAC (2.5 mg)-containing products, and that the use of these products should be contraindicated in patients with meningioma or history of meningioma. It is to be noted that for some products, e.g. Zoely, a contraindication and a warning on the risk of meningioma were already reflected in the PI, however, PRAC recommended further amendments to the previously agreed wording to reflect the current knowledge and be in alignment with the class. Additionally, for low dose CMA- or NOMAC containing products, a targeted follow-up questionnaire should be implemented (if not yet established) for cases of meningiomas, to ensure high-quality reports and facilitate causality assessment in future. Key elements for this targeted follow-up questionnaire were agreed by PRAC.

High-dose CMA (5-10 mg)- or high-dose NOMAC (3.75-5 mg)- containing products

Although meningioma has only been reported as a rare event with CMA-containing products, the causal relationship between meningioma and high dose CMA- or high dose NOMAC-containing products is considered established. Based on this, it is considered that the benefit-risk balance for treatment options with high dose-containing products should be restricted to situations where other interventions are considered inappropriate, and the treatment should be restricted to the lowest effective dose and shortest duration. Additionally, a contraindication in patients with meningioma or history of meningioma should be added to the PI, as well as a warning that symptoms of meningioma should be monitored and that treatment should be stopped if a patient is diagnosed with meningioma. In addition, PRAC recommended that information on results of the two epidemiological studies by Nguyen et al. should be reflected in the product information.

During the present review, PRAC considered the need to recommend MRI monitoring of patients before and regularly during the course of treatment with CMA or NOMAC. However, in view of the burden on individual patients and the very large number of MRIs to be performed to diagnose a single case of meningioma in a patient without any symptoms due to the low incidence of meningioma with use of CMA/NOMAC, PRAC considered that this measure would not be proportionate.

In view of the findings of the studies by Nguyen et al., healthcare professionals should be reminded via a direct healthcare professional communication (DHPC) of the warning and contraindication on the risk of meningioma for all products and be informed of the new restrictions for the use of high dose CMA- or NOMAC-containing products. The DHPC is to be jointly disseminated by marketing authorisation holders in each Member State. This communication should be distributed to endocrinologists, gynaecologists, general practitioners, learned societies and any other relevant target groups to be further defined at national level.

Finally, the PRAC considered the need for additional pharmacovigilance activities to evaluate the effectiveness of the proposed risk minimisation measures and was of the view that all marketing authorisation holders should analyse the prescribing behaviour and awareness of prescribers and evaluate the effectiveness of the newly introduced RMMs in the upcoming PSURs for the respective active substances.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for all chlormadinone acetate-containing products and nomegestrol acetate-containing products.
- The PRAC reviewed the available data on risk of meningioma during or following the use of medicinal products containing chlormadinone acetate or nomegestrol acetate, either alone or in combination, in particular the epidemiological studies including the French Health Insurance (CNAM) studies, as well as post-marketing case reports and data submitted by the marketing authorisation holders.
- The PRAC concluded from the data that the absolute risk of meningioma caused by treatment with products containing chlormadinone acetate or nomegestrol acetate use remains low. However, the risk increases with increasing cumulative doses and treatment duration of chlormadinone or nomegestrol acetate. PRAC also noted that risk of meningioma may decrease after treatment discontinuation.
- The PRAC therefore recommended that treatment with products containing high doses of chlormadinone acetate (5-10 mg) or nomegestrol acetate (3.75-5 mg) is restricted to situations where alternative treatments or interventions are considered inappropriate. Treatment should be limited to the lowest effective dose and shortest duration. Moreover

the Committee recommended that these high dose products, are contraindicated in patients with meningioma or history of meningioma.

- The PRAC also concluded that while no increased risk of meningioma was specifically identified following use of low dose chlormadinone acetate- or nomegestrol acetate-containing medicinal products, either alone or in combination, it is noted that there are situations where patients may be exposed to low dose products for a long period of time. Given that the risk increases with increasing cumulative doses of chlormadinone acetate or nomegestrol acetate, the Committee recommended that low dose chlormadinone acetate (1-2 mg)- or nomegestrol acetate (2.5 mg)-containing products should also be contraindicated in patients with meningioma or history of meningioma.
- The Committee recommended further updates to the product information of chlormadinone acetate-containing products and nomegestrol acetate-containing products to reflect current knowledge on the risk of meningioma.
- The Committee recommended that all marketing authorisation holders should evaluate the effectiveness of the newly introduced RMMs in the upcoming PSURs for the respective active substances.

In view of the above, the PRAC concluded that the benefit-risk balance of chlormadinone acetate-containing products and nomegestrol acetate-containing products remains favourable subject to changes to the product information described above.

A DHPC will be distributed to inform healthcare professionals of the above recommendations.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for chlormadinone acetate-containing products and nomegestrol acetate-containing products.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of nomegestrol-containing medicinal products and chlormadinone-containing medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore, the CHMP recommends the variation to the terms of the marketing authorisations for nomegestrol-containing medicinal products and chlormadinone-containing medicinal products.