1. NAME OF THE MEDICINAL PRODUCT

Zoely

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each white active tablet contains 57.71 mg of lactose monohydrate.
Each yellow placebo tablet contains 61.76 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 nomegestrol 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 6[1] 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

[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

that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative, a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: Temporary immobilisation including air travel > 4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Zoely has not been discontinued in advance.
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).

<u>Symptoms of VTE (deep vein thrombosis and pulmonary embolism)</u>

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 17β-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 reinstitution of Zoely use a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and 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 nomegestrol acetate-estradiol combination (nomegestrol acetate 3.75 mg + 1.5 mg estradiol) in post-menopausal women. Concomitant use of rifampicin decreases the $AUC_{0-\infty}$ of nomegestrol acetate by 95 % and increases the $AUC_{0-tlast}$ of estradiol by 25 %. Concomitant use of ketoconazole (200 mg single dose) does not modify estradiol metabolism whereas increases in the peak concentration (85 %) and $AUC_{0-\infty}$ (115 %) of nomegestrol acetate were observed, which were of no clinical relevance. Similar conclusions are expected in women of childbearing potential.

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 nomegestrol 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 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
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		hyperhydrosis, 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

System organ class	Adverse reaction in MedDRA Term[1]			
	Very common	Common	Uncommon	Rare
General disorders and administration site conditions			irritability, oedema	hunger
Investigations		weight increased	hepatic enzyme increased	

[1]The most appropriate MedDRA term to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

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 17β-estradiol, an oestrogen identical to the endogenous human 17β-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 µg (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
Cellulose, microcrystalline
Crospovidone
Talc
Magnesium stearate
Silica, colloidal anhydrous

Tablet coating (white active film-coated tablets)
Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG 3350
Talc

Tablet coating (yellow placebo film-coated tablets)

Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG 3350
Talc
Iron oxide yellow
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30˚C.

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 and 84 (3 x 28) 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. MANUFACTURER:

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

8. LICENSE HOLDER:

Truemed Ltd,
10 Beni Gaon St., Netanya 4250499.

9. REGISTRATION NUMBER:

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