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**

White active film-coated tablets: Each film-coated tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate).

Yellow placebo film-coated tablets: The tablet does not contain active substances.

Excipient:
Each white active film-coated tablet contains 57.71 mg of lactose monohydrate.
Each yellow placebo film-coated tablet contains 61.76 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablet (tablet).
Active film-coated tablets: white, round and coded ‘ne’ on both sides.
Placebo film-coated tablets: yellow, round and coded ‘p’ on both sides.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Oral contraception.

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).

**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 natural cycle (i.e. the first day of her menstrual bleeding). When doing so, no additional contraceptive measures are necessary.

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

The woman should start with Zoely preferably on the day after the last active tablet (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 tablet-taking.

*Following first-trimester abortion*

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

*Following delivery or second-trimester abortion*

Women should be advised to start between day 21 and 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method 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 12 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 she is more than 12 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 user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier
method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

**Day 8-17**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. 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 for 7 days.

**Day 18-24**

The risk of reduced reliability is imminent because of the forthcoming 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. **Method 1**
   - The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 4 placebo tablets from the last row must be discarded. The next blister pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. **Method 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 up to 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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

Yellow placebo tablets missed

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

**Advice in case of 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, a new tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, 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 bleed and may experience breakthrough-bleeding and spotting during the subsequent pack (just as when delaying a period).

**4.3 Contraindications**
COCs should not be used in the presence of any of the conditions listed below. As no epidemiological data are yet available with 17β-estradiol containing COCs, the contraindications for ethinylestradiol containing COCs are considered applicable to the use of Zoely. Should any of the conditions appear for the first time during Zoely use, the medicinal product should be stopped immediately.

- Hypersensitivity to the active substances or to any of the excipients of Zoely.
- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism).
- Presence or history of arterial thrombosis (e.g. myocardial infarction) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- Presence or history of cerebrovascular accident.
- History of migraine with focal neurological symptoms.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4) such as:
  - diabetes mellitus with vascular symptoms;
  - severe hypertension;
  - severe dyslipoproteinemia.
- Hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C (APC) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocystinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions/risk factors mentioned below is present, the benefits of the use of Zoely should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using Zoely. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether the use of Zoely should be discontinued. All data presented below are based upon epidemiological data obtained with COCs containing ethinylestradiol. Zoely contains 17β-estradiol. As no epidemiological data are yet available with estradiol containing-COCs, the warnings are considered applicable to the use of Zoely.

Circulatory disorders

- The use of any COC (including Zoely) carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive.
- Epidemiological studies have shown that the incidence of VTE in women with no known risk factors for VTE who use low dose oestrogen (<50 µg ethinylestradiol) combined oral contraceptives ranges from about 20 cases per 100,000 woman-years (for levonorgestrel-containing COCs) to 40 cases per 100,000 woman-years (for desogestrel/gestodene-containing COCs). This compares with 5 to 10 cases per 100,000 woman-years for non-users and 60 cases per 100,000 pregnancies. VTE is fatal in 1-2 % of cases. It is not known how Zoely influences this risk compared with other COCs.
- Epidemiological studies have also associated the use of COCs with an increased risk for arterial (myocardial infarction, transient ischaemic attack) thromboembolism.
• Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

• Symptoms of venous or arterial thrombosis or of a cerebrovascular accident can include: unusual unilateral leg pain and / or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen.

• The risk of venous thromboembolic events in COC users increases with:
  - increasing age;
  - a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
  - prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if COC use has not been discontinued in advance.
  - obesity (body mass index over 30 kg/m²).

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

• The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with:
  - increasing age;
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use a COC);
  - dyslipoproteinemia;
  - obesity (body mass index over 30 kg/m²);
  - hypertension;
  - migraine;
  - valvular heart disease;
  - atrial fibrillation;
  - a positive family history (arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

• Other medical conditions, which have been associated with adverse circulatory events, include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell disease.

• The increased risk of thromboembolism in the puerperium must be considered (for information on ‘Pregnancy and lactation’ see section 4.6).

• An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of Zoely use. Women using COCs should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate contraception should be initiated because of the teratogenicity of anti-coagulant therapy (coumarins).

**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 µg 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.

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.

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

• Worsening of depression, Crohn’s disease and ulcerative colitis 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.

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

Medical examination/consultation

Prior to the initiation or reinstitution of COC use a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). The woman should also be instructed to carefully read the user
leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman. Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

**Reduced efficacy**

The efficacy of COCs may be reduced in the event of e.g., missed tablets (see section 4.2), gastrointestinal disturbances during active tablet-taking (see section 4.2) or use of concomitant medicinal products (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).

**4.5 Interaction with other medicinal products and other forms of interaction**

**Interactions**

Influence of other medicinal products on Zoely

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

Examples of active substances that induce hepatic enzymes and thus result in increased clearance of sex hormones are: phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, and medicinal products or herbal preparations containing St. John’s wort, and, to a lesser extent, oxcarbazepine, topiramate, felbamate, and griseofulvin. Also HIV protease inhibitors with an inducing potential (e.g. ritonavir and nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine and efavirenz), may affect hepatic metabolism.

With hepatic enzyme-inducing substances, a barrier method should be used during the time of concomitant medicinal product administration and for 28 days after their discontinuation. In case of
long-term treatment with hepatic enzyme-inducing substances another method of contraception should be considered.

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\textsubscript{0-\textinfty} of nomegestrol acetate by 95 % and increases the AUC\textsubscript{0-t\text{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\textsubscript{0-\textinfty} (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**
Oral contraceptives may affect the metabolism of other medicinal products. Special attention should be paid to the interaction with lamotrigine.

**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.

**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).

**Breastfeeding**

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.

Breastfeeding 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 nursing mother has completely weaned her child and an alternative contraceptive method 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**

No studies on the effects on the ability to drive and use machines have been performed with Zoely. However, no effects on ability to drive and use machines have been observed in users of COCs.
4.8 Undesirable effects

*Summary of the safety profile*

Six multi-center 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.

*Tabulated summary of adverse reactions*

Possibly related adverse reactions that have been reported in users of Zoely are listed in the table below.

All adverse reactions are listed by system organ class and frequency; very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td>increased appetite, fluid retention</td>
<td>decreased appetite</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>decreased libido, depression/ depressed mood, mood altered</td>
<td></td>
<td></td>
<td>increased libido</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache, migraine</td>
<td></td>
<td></td>
<td>disturbance in attention</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td>contact lens intolerance/dry eye</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>hot flush</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>nausea</td>
<td>abdominal distension</td>
<td>dry mouth</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>cholelithiasis, cholecystitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>acne</td>
<td>hyperhydrosis, alopecia, pruritus, dry skin, seborrhea</td>
<td>chloasma, hypertrichosis</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>sensation of heaviness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>abnormal withdrawal bleeding</td>
<td>metrorrhagia, menorrhagia, breast pain, pelvic pain</td>
<td>hypomenorrhoea, breast swelling, galactorrhoea, uterine spasm, premenstrual syndrome, breast mass, dyspareunia, vulvovaginal dryness</td>
<td>vaginal odour, vulvovaginal discomfort</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>irritability, oedema</td>
<td>hunger</td>
<td></td>
</tr>
</tbody>
</table>
### Description of selected adverse reactions

A number of adverse reactions have been reported in women using combined oral contraceptives containing ethinylestradiol, which are discussed in more detail in section 4.4.

#### 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.

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-gonadotrophic activity, a progesterone receptor-mediated anti-estrogenic activity, a moderate anti-androgenic activity, and is devoid of any estrogenic, androgenic, glucocorticoid or mineralocorticoid activity.

The estrogen contained in Zoely is 17\(\beta\)-estradiol, a natural estrogen identical to the endogenous human 17\(\beta\)-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.

In two randomized, 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 \(\mu\)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:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse reaction in MedDRA Term(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight increased</td>
</tr>
</tbody>
</table>
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 randomized, 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 feces. Approximately 80% of the dose is excreted in urine and feces within 4 days. Excretion of nomegestrol acetate was nearly complete after 10 days and amounts excreted were higher in feces 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. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol circulates in the blood bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% 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 estrogen 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

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.

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.

5.3 Preclinical safety data

Repeat dose toxicity studies with estradiol, nomegestrol acetate or combination have indicated expected estrogenic and gestagen effects. Reproductive toxicity studies performed with the combination have shown foetotoxicity which is consistent with estradiol exposure.
Genotoxicity and carcinogenicity studies were not conducted with the combination. Nomegestrol acetate is not genotoxic. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core (white active and yellow placebo film-coated tablets)
- Lactose monohydrate
- Cellulose, microcrystalline (E460)
- Crospovidone (E1201)
- Talc (E553b)
- Magnesium stearate (E572)
- Silica, colloidal anhydrous

Tablet coating (white active film-coated tablets)
- Poly(vinyl alcohol) (E1203)
- Titanium dioxide (E171)
- Macrogol 3350
- Talc (E553b)

Tablet coating (yellow placebo film-coated tablets)
- Poly(vinyl alcohol) (E1203)
- Titanium dioxide (E171)
- Macrogol 3350
- Talc (E553b)
- Ferric oxide yellow (E172)
- Ferric oxide black (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 condition.

6.5 Nature and contents of container

PVC/aluminium blister containing 28 film-coated tablets (24 white film-coated tablets and 4 yellow film-coated 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 tablet may have harmful effects if reaching the aquatic environment. The tablets should be returned to a pharmacy or disposed of in
another safe way according to local requirements. These measures will help to protect the environment.

7. MARKETING AUTHORISATION HOLDER

Merck Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURING AUTHORITY RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Organon (Ireland) Ltd.
Drynam Road
Swords
Co. Dublin
Ireland

B. CONDITIONS OF THE MARKETING AUTHORIZATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORIZATION HOLDER

Medicinal product subject to medical prescription.

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

Not applicable.

- OTHER CONDITIONS

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 6.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached.
- At the request of the Agency.
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).

3. **LIST OF EXCIPIENTS**

   Contains lactose monohydrate
   See leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

   28 film-coated tablets
   84 (3 x 28) 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 REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight 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

Marketing Authorisation Holder:
Merck Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000 28 film-coated tablets
EU/0/00/000/000 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zoely
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

Merck Serono Europe Ltd.

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
Choose the day label that begins with your starting day.
Place the label on the blister over the words ‘Place day label here’.

<table>
<thead>
<tr>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
</tr>
<tr>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
</tr>
<tr>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
</tr>
<tr>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
</tr>
<tr>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
</tr>
<tr>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
</tr>
<tr>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
</tr>
<tr>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
</tr>
<tr>
<td>THU</td>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
</tr>
<tr>
<td>FRI</td>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
</tr>
<tr>
<td>SAT</td>
<td>SUN</td>
<td>MON</td>
<td>TUE</td>
<td>WED</td>
<td>THU</td>
<td>FRI</td>
</tr>
</tbody>
</table>

[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
1. **WHAT ZOEYL 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 nomegestrol acetate (a progestogen) and estradiol (an oestrogen).
- The 4 yellow 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’.
- Estradiol, the oestrogen in Zoely, is identical to the hormone produced by your ovaries during a menstrual cycle.
- Nomegestrol acetate, the progestogen in Zoely, is derived from the hormone progesterone. Progesterone is produced by your ovaries during a menstrual cycle.
2. BEFORE YOU USE ZOELY

General notes
Before you can begin taking Zoely, your doctor will ask you some questions about your personal health history and that of your close relatives. The doctor will also measure your blood pressure and, depending upon your personal situation, may also carry out some other tests.

In this leaflet, several situations are described where you should stop taking the pill, or where the reliability of the pill may be decreased. In such situations you should not have sexual intercourse 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 can be unreliable 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 HIV infection (AIDS) or any other sexually transmitted disease.

Do not use Zoely
In some situations you should not use a combined pill.
Tell your doctor if any of the following conditions applies to you before starting to use Zoely. Your doctor may then advise you to use a different (non-hormonal) method of birth control:

- if you are allergic (hypersensitive) to estradiol or nomegestrol acetate, or any of the other ingredients of Zoely;
- if you have (or have ever had) a blood clot in a blood vessel (venous thrombosis) of your legs, lungs (pulmonary embolus) or other organs. For possible signs of a blood clot see in section 2 ‘Blood clots (Thrombosis)’;
- if you have ever had a heart attack or a stroke;
- if you have (or have ever had) a condition that may be a first sign of a heart attack (such as angina pectoris which causes severe chest pain) or stroke (such as transient ischaemic attack [a TIA – a slight temporary stroke]);
- if you have a disease that may increase the risk of a clot in the arteries. This applies to the following diseases:
  - diabetes with damaged blood vessels
  - very high blood pressure
  - a very high level of fat in the blood (cholesterol or triglycerides);
- if you have a disorder affecting your blood clotting - for instance, protein C deficiency;
- if you have (had) a type of migraine called ‘migraine with aura’;
- if you have (had) inflammation of the pancreas (pancreatitis) associated with high levels of fat in your blood;
- if you have (had) severe liver disease and your liver is not yet working normally;
- if you have (had) a benign or malignant tumour in the liver;
- if you have (had), or if you may have, cancer of the breast or the genital organs;
- if you have any unexplained bleeding from the vagina.

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.

Take special care with Zoely

When should you contact your doctor
Contact your doctor as soon as possible:

- if you 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);
• if you feel a lump in your breast;
• if you experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives together with difficulty breathing;
• if you are going to use other medicines (see also in section 2 ‘Using other medicines’);
• if you are to be immobilised or are to have surgery (tell your doctor at least four weeks in advance);
• if you have unusual, heavy vaginal bleeding;
• if you forgot two tablets or more in the first week of the blister pack and had intercourse in the seven days before (see also in section 3 ‘If you forget to take Zoely’);
• if you have severe diarrhoea;
• if you 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’).

Stop taking tablets and contact your doctor immediately if you notice possible signs of a blood clot. The symptoms are described in section 2 ‘Blood clots (Thrombosis)’.

In some situations you need to take special care while using a combined pill. Tell your doctor if any of the following conditions apply to you. Also if the condition develops, or gets worse while you are using Zoely, you must tell your doctor.

• if you have hereditary 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. Products containing oestrogens may induce or worsen symptoms of angioedema;
• if a close relative has or has ever had breast cancer;
• if you have epilepsy (see in section 2 ‘Using other medicines’);
• if you have liver disease (for instance jaundice) or gallbladder disease (for instance gallstones);
• if you have diabetes;
• if you have depression;
• if you have Crohn’s disease or ulcerative colitis (chronic inflammatory bowel disease);
• if you have SLE (systemic lupus erythematosus; a disease affecting your natural defense system);
• if you have HUS (haemolytic uraemic syndrome; a disorder of blood clotting causing failure of the kidneys);
• if you have sickle cell anaemia (an inherited disease of the red blood cells);
• if you have elevated fatty acid levels in the blood (hypertriglyceridaemia) or a positive family history for this condition (familiarly hypertriglyceridaemia). If so, you may be at an increased risk of developing pancreatitis (inflammation of the pancreas) when using combined pills;
• if you have a condition that occurred for the first time or worsened during pregnancy or previous use of sex 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] (see in section 2 ‘When should you contact your doctor’);
• if you have (or have ever had) chloasma [yellowish-brown pigment patches, so called ‘pregnancy patches’, particularly on the face]. If so, avoid too much exposure to the sun or ultraviolet light;
• if you need an operation, or if you are off your feet for a long time (see in section 2 ‘Blood clots (Thrombosis)’).

**Blood clots (thrombosis)**

**Blood clots in a vein**

A blood clot in a vein (known as a ‘venous thrombosis’) can block the vein. This can happen in veins of the leg, the lung (a lung embolus), or any other organ.

Using a combined pill increases a woman’s risk of developing such clots compared with a woman not taking any combined pill. The risk of developing a blood clot in a vein is highest during the first year a woman uses the pill. The risk is not as high as the risk of developing a blood clot during pregnancy.
The risk of blood clots in a vein in users of a combined pill increases further:

- with increasing age;
- if one of your close relatives has had a blood clot in the leg, lung or other organ at a young age;
- if you are overweight;
- if you must 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 plaster cast.

If this applies to you, it is important to tell your doctor that you are using Zoely, as the treatment may have to be stopped. Your doctor may tell you to stop using your hormonal contraception several weeks before surgery or while you are less mobile. Your doctor will also tell you when you can start using Zoely again after you are back on your feet.

**Blood clots in an artery**

A blood clot in an artery can cause serious problems. For example, a blood clot in an artery in the heart may cause a heart attack, or in the brain may cause a stroke.

The use of a combined pill has been connected with an increased risk of clots in the arteries. This risk increases further:

- with increasing age;
- if you smoke.

When using a hormonal contraceptive like Zoely you are strongly advised to stop smoking, especially if you are older than 35 years;

- if you are overweight;
- if you have high blood pressure;
- if a close relative has had a heart attack or stroke at a young age;
- if you have a high level of fat in your blood (cholesterol or triglycerides);
- if you get migraines;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm).

**Symptoms of blood clots**

Stop taking tablets and see your doctor immediately if you notice possible signs of a blood clot, such as:

- an unusual sudden cough;
- severe pain in the chest which may reach the left arm;
- breathlessness;
- any unusual, severe, or long-lasting headache or worsening of migraine;
- partial or complete loss of vision, or double vision;
- slurring or speech disability;
- sudden changes to your hearing, sense of smell, or taste;
- dizziness or fainting;
- weakness or numbness in any part of your body;
- severe pain in your abdomen;
- severe pain or swelling in either of your legs.

Following a blood clot, recovery is not always complete. Rarely serious permanent disabilities may occur or the blood clot may even be fatal.

Directly after giving birth, women are at an increased risk of blood clots so you should ask your doctor how soon after delivery you can start taking a combined pill.

**Cancer**

Breast cancer has been found slightly more often in women using combined pills, but it is not known whether this is caused by the combined pills. For example, it may be that tumours are found more in women on combined pills because they are examined by the 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 ‘Take special care with Zoely’).

In rare cases, benign (noncancerous) liver tumours, and in even fewer cases malignant (cancerous) liver tumours have been reported 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 a long time. It is unknown if this finding is due to the use of hormonal contraceptives or to other factors, such as difference in sexual behaviour.

**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.

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

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines. Also tell any other doctor or dentist who prescribes another medicine (or the dispensing pharmacist) that you use Zoely. They can tell you if you need to take additional contraceptive precautions (barrier method) and, if so, for how long.

- 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 infections (e.g. ritonavir, nevirapine, nelfinavir, efavirenz);
  - other infectious diseases (e.g. griseofulvin);
  - high blood pressure in the blood vessels in the lungs (bosentan).

- The herbal product St. John’s wort 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 consult your doctor first.

- 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.

**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 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, please seek the advice of your doctor.

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

**Driving and using machines**
Zoely is unlikely to affect your ability to drive or use machines.

**Important information about some of the ingredients of Zoely**
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**

**When and how to take the tablets**
The Zoely blister contains 28 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’. Stick 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 the last white active tablet and may not have finished before the next blister is started.
Start taking your next blister immediately after the last yellow 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 users may not have their period every month during the intake of the yellow 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*

**When no hormonal contraceptive has been used in the past month**
Start taking Zoely on the first day of your cycle (i.e. the first day of your menstrual bleeding). Zoely will work immediately. You do not need to use an additional contraceptive method.

**When changing from another combined hormonal contraceptive (combined pill, vaginal ring, or transdermal patch)**
You can start taking Zoely the day after you have taken the last tablet from 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 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 use a vaginal ring or transdermal patch, it is best to start using 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.

**When changing from a progestogen-only pill (minipill)**
You can stop taking the minipill any day and start taking Zoely the next day. 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.

**When changing from a progestogen-only injectable, implant or a hormone-mediated 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 should also use a barrier method of contraception during the first 7 days of Zoely use. If, after having a baby, you have had sexual intercourse before starting Zoely, be sure that you are not pregnant or wait until the next menstrual period. If you want to start Zoely after having a baby and are breast-feeding, see also section 2 ‘Pregnancy and Breast-feeding’.

Ask your doctor 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 harmful effects from taking too many Zoely tablets at one time. If you have taken several tablets at a time, you may have nausea, vomiting or vaginal bleeding. If you discover that a child has taken Zoely, ask your doctor for advice.

If you forget to take Zoely
The following advice only refers to missed white active tablets.

- if you are less than 12 hours late in taking a tablet, the reliability of the pill is maintained. Take the tablet as soon as you remember and take the next tablets at the usual time.
- if you are more than 12 hours late in taking any tablet, the reliability of the pill may be reduced. The more consecutive tablets you have missed, the higher the risk that the contraceptive efficacy is decreased. 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 last white active missed tablet as soon as you remember (even if this means taking two tablets at the same time) and take the next tablet at the usual time. However, use a barrier method as an extra precaution for the next 7 days.
If you had sexual intercourse in the week before missing the tablets, there is a possibility of becoming pregnant. So 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. The protection against pregnancy is not reduced, and you do not need to take extra precautions. However, if you have missed more than 1 tablet, you should use extra precautions for 7 days.

Day 18-24 of white active tablet intake (see picture and schedule)
There is a particularly high risk of 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.
Two options can be followed:
Option 1)
Take the last missed white active 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. 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 spotting (drops or flecks of blood) or breakthrough bleeding while taking the white active tablets.
Option 2)
Stop taking the white active tablet immediately and go directly to the yellow placebo tablet interval. At the end of the placebo tablet interval, start with the next blister.

If you cannot remember how many white active tablets you have missed, follow the first option, use a barrier method as a precaution for the next 7 days and contact your doctor.
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. Consult your doctor before you start with the next blister.
Yellow placebo tablets missed
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 reliability of Zoely is maintained. Throw away the yellow placebo tablet(s) you missed and continue taking the next tablets at the usual time.

Schedule: if you are more than 12 hours late taking white 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, the active ingredients of your Zoely tablet 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 12 hours of when you normally take your pill. If this is not possible or 12 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 tablet, the reliability of Zoely is maintained.

If you want to delay your period
You can delay your period by not taking the yellow placebo tablets and going straight to a new blister of Zoely. You may experience 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. After finishing the 4 yellow placebo tablets from the second blister, start with the next (third) blister.

**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 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 some spotting (drops or flecks of blood) or breakthrough bleeding on white active tablet-taking days.

*If you are not sure what to do, consult your doctor.*

**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 ‘Using other medicines’.
- 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, you are recommended to wait until you have had a natural period before trying to conceive. 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 or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Zoely can cause side effects, although not everybody gets them. Contact your doctor if you notice any side effect, especially if severe or persistent, or if there is a change in your health that you think might be caused by the pill. Serious side effects seen with the pill, as well as the related symptoms, are described in section 2 ‘Blood clots (Thrombosis)’ and ‘Cancer’.

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

**Very common** (affects more than 1 user in 10):

- acne
- changes to menstrual periods (e.g. absence or irregularity)
Common (affects 1 to 10 users in 100):
• 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 (affects 1 to 10 users in 1,000):
• increased appetite; fluid retention (oedema)
• hot flush
• swollen abdomen
• 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 intercourse; dryness in the vagina or vulva; spasm of the uterus
• irritability
• increased liver enzymes

Rare (affects 1 to 10 users in 10,000):
• 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

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’.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE ZOELY

Keep out of the reach and sight of children.

Do not use Zoely 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 ingredients 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. FURTHER INFORMATION

What Zoely contains
The active substances are:
in the white active film-coated tablets: Each tablet contains 2.5 mg nomegestrol acetate and 1.5 mg estradiol (as hemihydrate).
in the 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, cellulose microcrystalline (E460), crospovidone (E1201), talc (E553b), magnesium stearate (E572) and silica colloidal anhydrous
- Tablet coating (white active film-coated tablets):
  Poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 and talc (E553b)
- Tablet coating (yellow placebo film-coated tablets):
  Poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), iron oxide yellow (E172) and iron oxide black (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 1 or 3 blisters of 28 film-coated tablets (24 white active film-coated tablets and 4 yellow placebo film-coated tablets) packed in a ply carton.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Merck Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

Manufacturer
Organon (Ireland) Limited
Drynam Road
Swords
Co. Dublin
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:
<table>
<thead>
<tr>
<th>Country</th>
<th>Company Name</th>
<th>Contact Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deutschland</td>
<td>MSD SHARP &amp; DOHME GMBH</td>
<td>Tel: +49 (0) 89 4561 2612</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:Infocenter@msd.de">Infocenter@msd.de</a></td>
</tr>
<tr>
<td>Norge</td>
<td>MSD (Norge) AS</td>
<td>Tel: + 47 32 20 73 00</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msdnorge@msd.no">msdnorge@msd.no</a></td>
</tr>
<tr>
<td>Österreich</td>
<td>Merck Sharp &amp; Dohme Ges.m.b.H.</td>
<td>Tel: +43 (0) 1 26 044</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msd-medizin@merck.com">msd-medizin@merck.com</a></td>
</tr>
<tr>
<td>Eesti</td>
<td>Merck Sharp &amp; Dohme OÜ</td>
<td>Tel: + 372 613 97 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msdeesti@merck.com">msdeesti@merck.com</a></td>
</tr>
<tr>
<td>Polska</td>
<td>MSD Polska Sp.z o.o.</td>
<td>Tel.: +48 22 549 51 00</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msdpolska@merck.com">msdpolska@merck.com</a></td>
</tr>
<tr>
<td>España</td>
<td>MERCK S.L.</td>
<td>Tel: + 34-917 454 400</td>
</tr>
<tr>
<td>France</td>
<td>LABORATOIRE THERAMEX</td>
<td>Tél: + 377 92 05 08 08</td>
</tr>
<tr>
<td>România</td>
<td>Merck Sharp &amp; Dohme Romania S.R.L.</td>
<td>Tel: + 402 1 529 29 00</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msdromania@merck.com">msdromania@merck.com</a></td>
</tr>
<tr>
<td>Ireland</td>
<td>Merck Sharp and Dohme Ireland (Human Health)</td>
<td>Tel: +353 (0)1 2998700</td>
</tr>
<tr>
<td></td>
<td>Limited</td>
<td><a href="mailto:medinfo_ireland@merck.com">medinfo_ireland@merck.com</a></td>
</tr>
<tr>
<td>Slovenija</td>
<td>Merck Sharp &amp; Dohme, inovativna zdravila d.o.o.</td>
<td>Tel: + 386 1 5204201</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msd_slovenia@merck.com">msd_slovenia@merck.com</a></td>
</tr>
<tr>
<td>Ísland</td>
<td>Vistor hf.</td>
<td>Simi: + 354 535 7000</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:ISmail@merck.com">ISmail@merck.com</a></td>
</tr>
<tr>
<td>Italia</td>
<td>Piazza del Pigneto 9</td>
<td>I-00176 Roma</td>
</tr>
<tr>
<td></td>
<td>Tel: + 39-0670384356</td>
<td></td>
</tr>
<tr>
<td>Kύπρος</td>
<td>Merck Sharp &amp; Dohme Cyprus Limited</td>
<td>Tηλ.: 800 00 673</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+357 22866700</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:cyprus_info@merck.com">cyprus_info@merck.com</a></td>
</tr>
<tr>
<td>Latvija</td>
<td>SIA Merck Sharp &amp;Dohme Latvija</td>
<td>Tel: + 371-67 364224</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:msd_lv@merck.com">msd_lv@merck.com</a></td>
</tr>
<tr>
<td>Suomi/Finland</td>
<td>MSD Finland Oy</td>
<td>Puh/Tel: + 358 (0)9 804650</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:info@msd.fi">info@msd.fi</a></td>
</tr>
<tr>
<td>Sverige</td>
<td>Merck Sharp &amp; Dohme (Sweden) AB</td>
<td>Tel: + 46-(0)77 5700488</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:medicinskinfo@merck.com">medicinskinfo@merck.com</a></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Merck Sharp &amp; Dohme Limited</td>
<td>Tel: + +44 (0) 1992 467272</td>
</tr>
<tr>
<td></td>
<td></td>
<td><a href="mailto:medicalinformationuk@merck.com">medicalinformationuk@merck.com</a></td>
</tr>
</tbody>
</table>
This leaflet was last approved in.

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