PRODUCT INFORMATION
ZOELY®

NAME OF THE MEDICINE

ZOELY
Each blister strip consists of 24 white active tablets each containing 2.5mg nomegestrol acetate and 1.5 mg oestradiol (as hemihydrate) and 4 yellow placebo tablets that do not contain active substances.

Nomegestrol acetate

Chemical name: 17α-acetoxy-6-methyl-19-norpregna-4,6-dien-3,20-dione
Molecular formula: C_{23}H_{30}O_{4}
Molecular mass: 370.48
CAS No.: 58652-20-3

Oestradiol

Chemical name: estra-1,3,5(10)-triene-3,17β-diol
Molecular formula: C_{18}H_{24}O_{2}
Molecular mass: 281.4
CAS No.: 50-28-2

DESCRIPTION

ZOELY is a combined oral contraceptive (COC) preparation containing the progestogen nomegestrol acetate and the natural oestrogen 17β-oestradiol as the active substances.
Nomegestrol acetate: a white to off white crystalline powder that is freely soluble in methylene chloride, acetone and ethyl acetate, soluble in dioxane and acetonitrile and sparing soluble in methanol and ethanol. Melting range is between 177 and 180°C.

Oestradiol: a white to almost white, crystalline powder and is practically insoluble in water. Melting range is between 173 and 179°C.

**PHARMACOLOGY**

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

The oestrogen contained in ZOELY is 17β-oestradiol, a natural oestrogen identical to the endogenous human 17β-oestradiol (E2). This oestrogen differs from the oestrogen ethinylooestradiol used in other combined oral contraceptives (COC) by the lack of the ethinyl group in the 17alpha position. During use of ZOELY, the average E2 levels are comparable to the E2 levels during the early follicular and late luteal phase of the menstrual cycle.

The contraceptive effect of ZOELY is based on the interaction of various factors, the most important of which are the inhibition of ovulation and the changes in the cervical secretion. During the use of ZOELY, nomegestrol acetate is primarily responsible for the suppression of ovulation, with 17β-oestradiol enhancing the suppressive effects of nomegestrol acetate.

After discontinuation of ZOELY, rapid return to ovulation was observed in most women.

Folic acid is an important vitamin in the early phase of pregnancy. Folic acid serum levels remained unchanged during and after ZOELY treatment for 6 consecutive cycles as compared to baseline.

Pharmacotherapeutic group: progestagens and oestrogens, fixed combinations, ATC code: G03A A14.

**Pharmacokinetic properties**

Nomegestrol acetate (NOMAC)

*Absorption*  
Orally administered nomegestrol acetate (NOMAC) is rapidly absorbed. Maximum plasma concentrations of NOMAC of about 7 ng/mL are reached at 2 h after single administration. The absolute bioavailability of NOMAC after a single dose is 63%. Administration of ZOELY with a high fat meal increased the bioavailability of NOMAC by 27-29% which was not considered clinically relevant.
**Distribution**
Nomegestrol acetate (NOMAC) 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 NOMAC at steady state is $1645 \pm 576L$.

**Metabolism**
Nomegestrol acetate (NOMAC) is metabolized into several hydroxylated metabolites without progestagenic activity, by liver cytochrome P450 enzymes, mainly CYP2C8, CYP2C19, CYP3A4 and CYP3A5. NOMAC and its hydroxylated metabolites undergo extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The oestrogenic and androgenic activities of the metabolites are unknown. The apparent clearance at steady state is 26 L/h.

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

**Linearity**
Dose-linearity was observed in the range $0.625 – 5mg$ (assessed in fertile and post-menopausal women).

**Steady-State Conditions**
The pharmacokinetics of nomegestrol acetate (NOMAC) are not influenced by SHBG. Steady-state is achieved after 5 days. Maximum plasma concentrations of NOMAC of about 12 ng/mL are reached 1.5 hours after dosing. Average steady state plasma concentrations are 4 ng/mL.

**Drug-drug interactions**
From *in vitro* studies, nomegestrol acetate causes no notable induction or inhibition of any cytochrome P450 enzymes and has no clinically relevant interaction with the P-gp transporter.

**Oestradiol (E2)**

**Absorption**
$17\beta$-Oestradiol (E2) is subject to a substantial first-pass effect after oral administration. The absolute bioavailability is approximately 5%. After administration of ZOELY with a high fat meal, the mean exposure to oestradiol (E2) was only marginally affected. Exposure to the major metabolite of E2, estrone (E1), was increased by about 20% which was not considered clinically relevant.

**Distribution**
The distribution of exogenous and endogenous $17\beta$-oestradiol (E2) is similar. Oestrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Oestradiol circulates in the blood
bound to SHBG (37%) and to albumin (61%), while only approximately 1-2% is unbound.

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

**Elimination**
17β-Oestradiol (E2) 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 elimination half-life of E2, which is calculated to be 8.4 ± 6.4 hours, after intravenous administration.

**Steady-State Conditions**
Maximum serum concentrations of 17β-oestradiol (E2) are about 90 pg/mL and are reached 6 hours after dosing. Average serum concentrations are 50 pg/mL and these E2 levels correspond with the early and late phase of a woman’s menstrual cycle.

**Special Populations**

**Paediatric population**
Whole-body-physiologically based pharmacokinetic modeling and simulation showed that no difference in the nomegestrol acetate pharmacokinetics is expected between post-menarcheal adolescent women (aged 12-17 years) and adult women.

**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 metabolised in women with impaired liver function.

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

**CLINICAL TRIALS**

**Contraceptive efficacy**
Two randomized, open-label, comparative efficacy-safety trials (Study report 292001 and 292002) were conducted in more than 3200 women treated for 13 consecutive cycles with ZOELY. The primary efficacy and safety parameters were contraceptive efficacy, vaginal bleeding pattern (cycle control), general safety and acceptability. Women entering the study were aged between 18 and 50 years and women with a
BMI greater than 35 were excluded from the study. Women were excluded from the study if they had conditions which were listed as a contraindication for combined oral contraceptives. The overall Pearl Index (method failure and user failure) 18-50 years of age was: 0.64 (upper limit 95% CI 1.03).

In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

A randomized, open-label, comparative, multicenter trial (Study report 292004) was performed to assess effects of ZOELY on hemostasis, lipids, carbohydrate metabolism, adrenal and thyroid function and on androgens. Glucose tolerance and insulin sensitivity remained unaltered and no clinically relevant effects on lipid metabolism and hemostasis were observed with ZOELY. The comparator levonorgestrel 150μg + ethinylestradiol 30μg was associated with more pronounced changes in these parameters. ZOELY increased the carrier proteins TBG and CBG, but to lesser extent than LNG-EE. ZOELY induced a small increase in SHBG, which was slightly higher than LNG-EE (20 to 30 µg EE). The androgenic parameters androstenedione, DHEA-S, total and free testosterone were significantly reduced during use of ZOELY.

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.

INDICATIONS

Oral contraception.

CONTRAINDICATIONS

Combined hormonal contraceptives (COCs) should not be used in the presence of any of the conditions listed below. No epidemiological data are available with 17β-oestradiol containing COCs, but the contraindications for ethinylestradiol containing COCs are also considered applicable to the use of ZOELY. Should any of the conditions appear for the first time during the use of ZOELY, the product should be stopped immediately:

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

PRECAUTIONS

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 its use should be discontinued. All data presented below are based upon epidemiological data obtained with combined oral contraceptives (COCs) containing ethinyloestradiol. ZOELY contains 17β-oestradiol. No epidemiological data are available with oestradiol containing COC but the warnings are considered applicable to the use of ZOELY.

Circulatory Disorders
• Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.
• Use of any ethinyloestradiol-containing COC 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. This increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 per 100,000 pregnant woman years. This compares with 5 to 10 cases per 100,000 woman-years for non-users. VTE is fatal in 1%-2% of cases. It is not known how ZOELY influences this risk compared with other COCs.
• 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 can include: 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 thromboembolism 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 immobilization, 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 remobilization.
  - obesity (body mass index over 30 kg/m²);
  - and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thrombosis.

• The risk of arterial thromboembolic complications increases with:
  - increasing age;
  - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
  - 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 uraemic syndrome, chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and sickle cell disease.

• The increased risk of thromboembolism in the puerperium must be considered (see *Use in Pregnancy*).

• An increase in frequency or severity of migraine (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).

**Neoplasms**

• The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Epidemiological studies have indicated that long-term use of ethinyloestradiol-containing COCs contributes to this increased risk, but there continues to be uncertainty about the extent to which this finding is attributable to confounding effects, like increased cervical...
screening and difference in sexual behaviour including use of barrier contraceptives, or a causal association.

- With the use of the higher-dosed COCs (50 μg ethinyloestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to 17β-oestradiol-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 ethinyloestradiol-containing 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. In seven multi-centre clinical trials of up to two years duration, no clinically relevant changes in blood pressure were observed with ZOELY.
- 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 uremic syndrome; Sydenham’s chorea; herpes gestationis; otosclerosis related hearing loss; (hereditary) 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.
- There is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing <0.05 mg ethinyloestradiol). However, diabetic women should be carefully observed while taking a COC especially in the first months of use. ZOELY was shown to have no effect on peripheral
insulin resistance and glucose tolerance in healthy women (see Clinical Trials).

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

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 contraindications and precautions. 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 Dosage and Administration), gastro-intestinal disturbances during active tablet taking (see Dosage and Administration), or use of concomitant medication (see Interactions).

Cycle control
As with all COCs, breakthrough bleeding or spotting may occur, especially during the first months of use. Therefore, the evaluation of any breakthrough bleeding or spotting is only meaningful after an adaptation interval of about three cycles. 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. Women with undiagnosed abnormal vaginal bleeding should not start treatment with a COC until a possible underlying condition has been excluded.

In the pivotal efficacy and safety trials, women using ZOELY experienced overall a low number of bleeding events. Withdrawal bleedings were light and of short duration (on average 3-4 days) and often less painful (dysmenorrhea).

Some users of ZOELY have reported absence of withdrawal bleeding during the placebo yellow tablet phase although not being pregnant. In such cases, absence of withdrawal bleeding was not associated with a higher occurrence of breakthrough bleeding or spotting in the subsequent cycle.

If absence of withdrawal bleeding occurs and ZOELY is taken according to the instructions as described under Dosage and Administration 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 bleeds are missed.

Genotoxicity
No evidence for genotoxicity was found with nomegestrol acetate in assays for bacterial and mammalian mutagenicity, yeast mitotic gene conversion, chromosomal aberrations and unscheduled DNA synthesis \textit{in vitro} and clastogenicity \textit{in vivo} (mouse and rat bone marrow micronucleus tests).

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy and an increased incidence of sister chromatid exchanges (indicative of DNA damage) in mammalian cells. None of these effects were induced by oestradiol in human lymphocyte cultures. Importantly, there was no evidence for micronuclei formation in rodent bone marrow assays.

The genotoxic potential of the combination of nomegestrol acetate and oestradiol has not been investigated.

Carcinogenicity
Carcinogenicity studies have not been performed with the combination of nomegestrol acetate and oestradiol. However, studies have been performed for the two active components separately.

Supraphysiological doses of oestradiol have been associated with the induction of tumours in oestrogen-dependent target organs in all rodent species tested. The relevance of these findings with respect to humans has not been established. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

In a long-term oral (dietary) carcinogenicity study in mice, nomegestrol acetate increased the incidence of mammary gland carcinoma and pituitary adenoma in females at doses ≥20mg/kg/day and 50 mg/kg/day, respectively. Systemic exposure to nomegestrol acetate (plasma AUC) in animals at these doses was 4 to 15 times higher than that of women treated with ZOELY. These findings are consistent with extensive endocrine disruption in the species caused by the progestagenic activity of nomegestrol acetate.

No evidence of tumourigenicity was found with nomegestrol acetate in a 2-year study in rats using dietary doses up to 10 mg/kg/day (yielding 30 times the expected human exposure level).

Use in pregnancy (Category B3)
ZOELY is not indicated during pregnancy. If pregnancy occurs during treatment with ZOELY, further intake should be stopped. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used ethinyloestradiol-containing COCs prior to pregnancy, nor a teratogenic effect when ethinyloestradiol-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 rats, treatment with nomegestrol acetate and oestradiol in combination caused increased post-implantation loss, abortions, decreased fetal weight, feminisation of male fetuses, malformations (cleft palate and bent tail) and increased variations (vertebral and rib abnormalities and incomplete ossification). Nomegestrol acetate, given alone in rats, prolonged or impaired parturition. Post-implantation loss was increased and fetal weight was decreased in rabbits treated with the combination. Systemic exposure to nomegestrol acetate (plasma AUC) at no-effect doses in the animal embryofetal development studies was similar to or less than the expected human exposure level. Nomegestrol acetate was shown to cross the placenta in monkeys, with fetal plasm levels comparable to maternal drug levels.

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

**Paediatric use**
Warnings and precautions for post-menarcheal adolescents less than 18 years of age and women greater than 50 years of age are expected to be similar to those described for adults between these age groups although this has not been confirmed in clinical trials.

**Interactions with other medicines**
Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

**Influence of other medicinal products on ZOELY**
Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature for COCs in general.

**Hepatic metabolism:** Interactions can occur with drugs that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin, and products containing St. John’s wort). Also HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and combinations of them, have been reported to potentially affect hepatic metabolism. With microsomal enzyme-inducing drugs, a barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. In case of long-term treatment with microsomal enzyme inducing drugs another method of contraception should be considered. Drugs that inhibit microsomal enzymes (e.g. ketoconazole) may increase sex hormone plasma levels.
Antibiotics: Contraceptive failures of ethinyloestradiol-containing oral contraceptives have been reported with antibiotics, such as ampicillin and tetracyclines. The mechanism of this effect has not been elucidated and it is unknown whether interactions of antibiotics with a 17β-oestradiol-containing contraceptive occur. Women on treatment with antibiotics (except rifampicin and griseofulvin, see above) should use a barrier method until 7 days after discontinuation. If the period during which the barrier method is used extends beyond the end of the white tablets in the COC pack, the yellow placebo tablets must be discarded and the next COC pack should be started right away.

Drug interaction studies were not performed with ZOELY, but two studies with rifampicin and ketoconazole, respectively, were performed with a higher dosed NOMAC-E2 combination (NOMAC 3.75 mg + 1.5 mg E2) in post-menopausal women.

Influence of ZOELY on other medicinal products
Oral contraceptives may affect the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

Paediatric population
The interactions as described above are expected to be similar in postmenarcheal adolescent women.

Effect on 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.

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

ADVERSE EFFECTS

Tabulated summary of adverse reactions
Seven multi-centre clinical trials of up to two years duration were used to evaluate the safety of ZOELY. In total 3,490 women, aged 18-50, were enrolled and completed 35,028 cycles.

ZOELY is well tolerated and demonstrates an overall safety profile similar to other combined oral contraceptives. Possibly related undesirable effects that have been reported in users of ZOELY are listed in the table below:
<table>
<thead>
<tr>
<th>Body system</th>
<th>Very common ≥ 1/10</th>
<th>Common ≥ 1/100 to &lt;1/10</th>
<th>Uncommon ≥ 1/1000 to &lt; 1/100</th>
<th>Rare ≥1/10,000 to &lt; 1/1000</th>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<td></td>
<td>increased appetite, fluid retention</td>
<td>decreased appetite</td>
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<tr>
<td>Psychiatric disorders</td>
<td>decreased libido, depressed mood, mood altered</td>
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<td></td>
<td>increased libido</td>
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<td>Nervous system disorders</td>
<td>headache migraine</td>
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<td>disturbance in attention</td>
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<td>Eye disorders</td>
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<td></td>
<td>dry eye, contact lens intolerance</td>
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<td>hot flush</td>
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<td>Gastrointestinal disorders</td>
<td>nausea</td>
<td>Abdominal distension</td>
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<td>dry mouth</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>acne$^2$</td>
<td>hyperhydrosis, alopecia, pruritus, dry skin, seborrhea</td>
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<td>chloasma, hypertrichosis</td>
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<td>sensation of heaviness</td>
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<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>
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<td>General disorders and administrative site conditions</td>
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<td>irritability, oedema</td>
<td>hunger</td>
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<td>Investigations</td>
<td>weight increased</td>
<td>hepatic enzyme increased</td>
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</table>

1 The most appropriate MedDRA term (version 13.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

2 Acne was a solicited rather than spontaneously reported event, being assessed at every study visit.
The adverse reaction rates for Zoely (N = 3490) in comparison to the reference COC containing drospirenone 3 mg – ethinylestradiol 30 μg (21/7 regimen) (N = 1105) in the integrated safety data set were:
acne (15.4 % versus 7.9 %), weight increased (8.5 % versus 5.9 %) and abnormal withdrawal bleeding (predominantly absence of withdrawal bleeding) (10.2 % versus 0.6 %).

Description of selected adverse reactions
A number of undesirable effects have been reported in women using combined oral contraceptives containing ethinylestradiol, which are discussed in more detail in Precautions. These include:

- venous thromboembolic disorders;
- arterial thromboembolic disorders;
- hypertension;
- hormone-dependent tumours (e.g. liver tumours, breast cancer);
- chloasma.

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see Contraindications and Precautions.

Paediatric population
Frequency, type and severity of adverse reactions in post-menarcheal adolescents are expected to be the same as in adult women.

Other special populations
No studies have been performed with renally or hepatically impaired subjects. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

DOSAGE AND ADMINISTRATION

How to take ZOELEY
Tablet intake instructions are the same for all users.

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

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

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch)
The woman should start with ZOLEY 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 ZOLEY preferably on the day of removal, but at the latest when the next application would have been due.

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

Changing from a progestagen-only-method (minipill, implant, injectable) or from a hormone-medicated Intra Uterine System (IUS)
The woman may switch any day from the minipill and ZOLEY should be started on the next day. An implant or IUS may be removed any day, and ZOLEY should be started on the day of its removal. When changing from an injectable, ZOLEY 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
For breast-feeding women see Use in Lactation under Precautions.
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 for the first 7 days of white active tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets
The following advice only refers to missed white active tablets:
If the user 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.

### Missed tablet advice

**One white active tablet missed**
Contraceptive protection is not reduced. The user 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. She does not need any additional contraceptive protection.

**Two or more white active tablets missed**
If the woman missed two or more white tablets and subsequently has no withdrawal bleed while taking the yellow placebo tablets, the possibility of a pregnancy should be considered (see also ‘Cycle control’ under Precautions).

**Day 1-7**
The user 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. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered.

**Day 8-17**
The user 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. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking.
Day 18-24
The risk of reduced reliability is higher because of the forthcoming yellow placebo-tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. The user should take the last missed white tablet as soon as she remembers, even if this means taking two tablets at the same time. She should never take more than two white tablets at the same time. A barrier method should be used until she has completed 7 days of uninterrupted white tablet-taking. Thus, the next pack must be started the day after the white tablets in the current pack are finished, i.e., no yellow placebo tablets should be taken. The user is unlikely to have a withdrawal bleed until she takes the yellow tablets of the second pack, but she may experience breakthrough bleeding or spotting while taking white tablets.

Please note: If the user 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.

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, the tablet should be considered as missed. In case of one white tablet missed contraceptive protection is not reduced. If vomiting again takes place on the next day(s), the advice as given for 2 or more white tablets missed under Dosage and Administration (‘Management of missed tablets’) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra white tablet(s) from another pack.

How to shift periods or how to delay a period
To delay a period the woman should continue with another blister pack of ZOELY without taking the yellow tablets from her current pack. The extension can be carried on for as long as wished until the end of the white 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 women is used to with her current scheme, she can be advised to shorten her forthcoming 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).

OVERDOSAGE

There have been no reports of serious deleterious effects from 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.

PRESENTATION AND STORAGE CONDITIONS

Each blister of ZOELY contains:

- 24 white, round, film-coated tablets coded with ‘ne’ on both sides, each containing 2.5mg nomegestrol acetate and 1.5mg oestradiol. The tablets also contain the inactive ingredients lactose, cellulose microcrystalline, crospovidone, talc, magnesium stearate, silica colloidal anhydrous, polyvinyl alcohol, titanium dioxide and macrogol 3350.
- 4 yellow, round, film-coated tablets coded with ‘p’ on both sides. The tablets contain the inactive ingredients lactose, cellulose microcrystalline, crospovidone, talc, magnesium stearate, silica colloidal anhydrous, polyvinyl alcohol, titanium dioxide, macrogol 3350, iron oxide yellow E 172 and iron oxide black E 172.

Pack sizes: 1 x 28 and 3 x 28 tablets in PVC/aluminium blisters (transparent PVC thermoforming film with aluminium lidding foil). Not all pack sizes may be marketed.

The shelf life of ZOELY is 3 years when stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
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POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 15 August 2011.