1. NAME OF THE MEDICINAL PRODUCT

Zinnia P*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each of the 21 white tablets contains 30 µg ethinylestradiol and 150 µg levonorgestrel

The 7 yellow tablets are placebos

Excipients with known effect: lactose and sucrose

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Active tablets :
White, circular, biconvex, sugar coated tablets.

Placebo tablets :
Yellow, circular, biconvex, sugar coated tablets.

4. CLINICAL PARTICULARS

4.1 Indications

Contraception for women

4.2. Posology and method of administration

4.2.1 Posology and method of administration

The tablets should be taken every day at about the same time, if necessary with some liquid, in the sequence indicated on the blister pack. One tablet is to be taken daily over a period of 28 consecutive days. The next pack is started the day after the last tablet from the previous pack was taken. Two or three days after starting on the placebo tablets, withdrawal bleed usually begins, and this may still be continuing when the new pack has been started.

4.2.2 Starting to take Zinnia P

- When no hormonal contraceptives were taken in the previous month:

The course may be started on day 1 of the cycle (day 1 of menstruation). If alternatively the course is started on any other day of the cycle, an additional non-hormonal (barrier) method of contraception should be used during the first 7 days of taking the tablets.

- When changing from another combination product to hormonal contraception (combined oral contraceptive(COC), vaginal ring, transdermal patch):

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Depending upon the type of combined oral contraceptive used before Zinnia P is taken, the course should be started either on the day after the usual tablet-free interval, which follows the last active tablet, or on the day after the last placebo tablet of the combined oral contraceptive. If a vaginal ring or a transdermal patch was previously used, then Zinnia P should be started on the day after the usual interval, during which neither ring nor patch was used.

- When changing from a progestogen-only product (mini pill, injection preparation, implant) or from an intrauterine system (IUS)

When changing from a progestogen-only product, the switch can take place on any day. When changing from an implant or an intrauterine system, it should take place on the day of its removal, or, when switching from an injectable, on the day the next injection would have been due. In any event, an additional non-hormonal contraceptive method (barrier method) is necessary during the first 7 days of taking Zinnia P.

- Following a first or second trimester abortion

Zinnia P can be started immediately . In this case, no additional contraceptive precautions are necessary.

- Following delivery

Breast-feeding women

Zinnia P should not be used in the first 6 months of breast-feeding, as milk production may be reduced and small quantities of the active substances may pass into the milk. Zinnia P may be used by breast-feeding women after 6 months.

Non-breast-feeding women

Since the risk of a thromboembolic event is increased during the period directly following delivery, women who are not breast-feeding should not start taking oral contraceptives earlier than day 21 following delivery. A longer period of up to 42 days should be allowed when there are risk factors for venous thromboembolism (VTE), such as previous VTE, thrombophilia, immobility, transfusion at delivery, BMI > 30 kg/m^2, postpartum haemorrhage, history of pre-eclampsia, caesarean delivery, smoking.

During the first 7 days of taking Zinnia P, she should use an additional non-hormonal (barrier) contraceptive method. If she has already had sexual intercourse, pregnancy must be ruled out or she should wait for her first menstrual bleed before starting to take the product.

4.2.3 Duration of administration

Zinnia P can be used as long as a hormonal contraceptive method is desired and there are no health risks contraindicating it (see section 4.4 for regular checkups).

4.2.4 If a tablet has been missed

The contraceptive efficacy may be decreased if Zinnia P is not taken regularly.

The following two basic rules apply when a tablet has been missed:
1. Taking the active tablets must never be discontinued for more than 7 days.
2. The tablets should be taken regularly, without interruption, for seven days in order to attain an adequate suppression of the hypothalamic-pituitary-ovarian axis function.

Single delayed tablet

A single delayed tablet should be taken as soon as possible, even if two tablets have to be taken on the same day. If this can be done within 12 hours, contraceptive protection is maintained. All subsequent tablets should then be taken at the usual time.

If the user is more than 12 hours late taking the tablet, contraceptive protection is no longer assured. During the next 7 days, the woman should use an additional non-hormonal (barrier) contraceptive method. If the

user forgot to take only one active tablet once in week 2, then it is not necessary to take additional contraceptive precautions.
If the usual withdrawal bleed does not occur following the active tablets in the sequence with the forgotten tablet, pregnancy must be ruled out before a new blister pack is started.

More than one forgotten tablet
If the user forgot to take more than one active tablet, she should use an additional non-hormonal (barrier) contraceptive method, until the next usual withdrawal bleed appears.

1. If there are fewer than seven days between the forgotten tablets and the last active tablet in the present pack, then the user should start immediately, without taking the placebo tablets, with the first active tablet of the next blister pack. Therefore, the usual withdrawal bleed will probably not occur until all the active tablets from this second pack have been taken. An increase in breakthrough bleeding and spotting can occur, however.

2. Alternatively, the user can stop taking the active tablets and start taking the placebo tablets from the present pack. Following a placebo interval of up to seven days, including the days on which she forgot to take the tablets, the user then continues by taking the active tablets from the next pack.

Forgetting placebo tablets has no effect on contraceptive protection.

4.2.5 What to do in case of vomiting or diarrhoea

In the event of vomiting or severe diarrhoea within the first four hours after taking Zinnia P, the active substances may possibly not be completely absorbed. Therefore additional contraceptive measures should be used. The same instructions apply as in the case of forgotten tablets (see also sections 4.4 and 4.5). If the user wishes to keep to her accustomed tablet-taking schedule, the additional tablet has to be taken from another blister pack. She should use additional non-hormonal contraceptive methods and consult a doctor in the event of persistent or repeated gastro-intestinal disturbances.

4.2.6 Delaying the withdrawal bleed

In order to postpone the withdrawal bleed the user should continue taking tablets from the next pack of Zinnia P immediately, without taking any placebo tablets. The withdrawal bleed can be delayed for as long as desired by taking only the first 21 active tablets from each pack, though evidence for this is limited beyond 2 years. Increased breakthrough bleeding and spotting can occur during this time. Following the subsequent regular seven-day period of taking the placebo tablets , the user may continue to take Zinnia P as usual.

4.3 Contraindications

Combined oral contraceptives are contraindicated in the following instances:

– existing or any prior history of venous thrombosis (deep-vein thrombosis, pulmonary embolism), whether on anticoagulation therapy or not,
– existing or any prior history of arterial thrombosis (e.g. myocardial infarction) and its prodromal stages (e.g. transient ischemic attack, angina pectoris),
-systemic lupus erythematosis with positive (or unknown) antiphospholipid antibodies
-multiple co-existing risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes and hypertension,
– known predisposition to venous or arterial thromboses such as APC (activated protein C) resistance, antithrombin-III deficiency, factor V Leiden, protein-C deficiency, protein-S deficiency or to another

thrombogenic coagulopathy, a thrombogenic valvular heart disease or thrombogenic heart-rhythm disturbances.
– prior cerebrovascular insult,
– smoking (see section 4.4),
– hypertension above 160/100
– Diabetes mellitus with vascular changes,
– history of migraines with aura or focal neurological symptoms,
– existing or history of pancreatitis, when accompanied by severe hypertriglyceridemia
– existing or history of severe liver disease/uncompensated cirrhosis (also Dubin-Johnson and Rotor syndromes),
- acute hepatitis or flare (combined oral contraceptives should not be started during these; continuing use for those already taking combined oral contraceptives is usually possible)
– existing or history of hepatic tumours,
– known or suspected sex-hormone dependent, malignant tumours (e.g. of the breast or the endometrium),
– undiagnosed vaginal bleeding,
– undiagnosed amenorrhoea,
– hypersensitivity to the active substances or one of the other components of Zinnia P.

The presence of one or more risk factors related to venous or arterial diseases may constitute a contraindication, depending on the type and severity, (see section 4.4).

If one of these disorders occurs for the first time while using the combined oral contraceptive, the medicinal product must be discontinued immediately.

4.4 Special warnings and precautions for use

4.4.1 Reasons to discontinue taking Zinnia P immediately (in addition to the contraindications specified in section 4.3)

– pregnancy or suspected pregnancy,
– first signs of venous inflammation or signs of a possible thrombosis (also retinal thrombosis), embolism or myocardial infarction (see section 4.4.3.1),
– persistent high blood pressure with values exceeding 140/90 mmHg. The resumption of combined oral contraceptives can be considered when blood-pressure values have been normalised by treatment for hypertension.
– planned surgery (at least 4 weeks in advance) and/or longer periods of immobilisation (e.g. following accidents). The user should not resume taking the tablets until at least two weeks after complete remobilisation.
– first occurrence or increased severity of a migraine,
– if headaches occur unusually frequently, persistently or in unusual severity, and/or focal neurological symptoms suddenly develop (possible first signs of a stroke),
– severe pain in the epigastric region, enlargement of the liver or signs of intra-abdominal bleeding (possible indication of a liver tumour),
– occurrence of icterus, hepatitis, generalised pruritus, cholestasis, marked liver-function test elevations. (Steroid hormones are metabolised less effectively when the liver function is diminished.)
– acute complications of Diabetes mellitus
– new or recurrent porphyria.

4.4.2 Diseases / risk factors requiring special medical monitoring:

– heart and kidney diseases, since the active substance, ethinylestradiol, can cause fluid retention,
– superficial phlebitis, pronounced inclination to varicose veins, peripheral circulatory disturbances, since these can be associated with thromboses,
– increased blood pressure (above 140/90 mmHg),

– disturbances in lipid metabolism. Levonorgestrel, the progestogen portion of Zinnia P , can cause an increase in lower density lipoproteins (LDL). The dosage of an existing lipid-lowering therapy may need to be changed. Ethinylestradiol, the oestrogen portion, can cause pronounced increases in plasma triglycerides and subsequently pancreatitis and other complications in users with lipid metabolism disturbances (see section 4.3).
– sickle-cell anaemia,
– nodular hyperplasia of the liver,
- existing liver disease, acute hepatitis or flares
– gall-bladder disease,
– migraine,
– depression. It is not known if depression is associated with the use of Zinnia P. If necessary, other, non-hormonal contraceptive methods should be used.
– reduced glucose tolerance / Diabetes mellitus Since combined oral contraceptives can affect peripheral insulin resistance and glucose tolerance, it may be necessary to adjust doses of insulin or other antidiabetic agents.
– smoking, especially over age 35 and more than 15 cigarettes per day,
– epilepsy,
– Chorea minor (Sydenham's chorea),
– chronic-inflammatory intestinal diseases (Crohn's disease, ulcerative colitis),
– haemolytic-uraemic syndrome,
– Uterine myoma
– otosclerosis,
– prolonged immobilisation (also see section 4.4.1),
– obesity,
– systemic lupus erythematosis,
– women over 40.

4.4.3 Serious undesirable effects of combined oral contraceptives

The use of combined oral contraceptives is connected to an increased risk of various serious diseases, such as myocardial infarction, thromboembolism, stroke and hepatic neoplasia. The presence of other risk factors, such as increased blood pressure, hyperlipidaemia, obesity and diabetes additionally increases the morbidity and mortality risk.

Smoking while taking hormonal contraceptives increases the risk of serious cardiovascular events. The risk increases with increasing age and cigarette consumption. Women, particularly over age 30, should not smoke while using hormonal contraceptives. If smoking cessation cannot be achieved, other contraceptive methods should be used (see section 4.3).

4.4.3.1 Thromboembolic events and other vascular diseases

A) Cardiac infarction
Taking oral contraceptives is associated with an increased risk of myocardial infarction. This risk is highest in women with other risk factors for cardiovascular disease.

B) Cerebrovascular disease
Combined oral contraceptives increase both the relative and the absolute risk of cerebrovascular events (ischemic and haemorrhagic stroke). The risk is greatest in women over 35 years of age who have high blood pressure and who smoke.

Among the risk factors related to arterial thromboembolic complications are:

–smoking,
– increasing age,

– disturbances in lipid metabolism,
– obesity,
– hypertension
– Diabetes mellitus,
– heart valve disorders,
– atrial fibrillation,
– certain inherited or acquired thrombophilias (e.g. family history of arterial thromboses in siblings or parents relatively early in life)
– migraine, particularly with focal neurological symptoms.

If risk factors related to cardiovascular or cerebrovascular diseases are present, combined oral contraceptives should be used with caution (also see sections 4.4.1 and 4.4.2).

C) Venous thromboses and thromboembolism (VTE)

The use of a combined oral contraceptive increases the risk of VTE. The additional risk is at its highest during the first year of commencing use of a combined oral contraceptive. The increased risk when using a combined oral contraceptive is lower than the VTE risk during pregnancy, which is estimated at 60 cases per 100,000 pregnancies. In 1 to 2% of cases, a VTE results in death.

The absolute VTE risk (incidence) caused by combined oral contraceptives containing levonorgestrel with 30 µg ethinylestradiol is about 20 cases per 100,000 woman-years.

There are reports of a 2-to-4-fold increase in the relative risk of post-operative thromboembolic complications when using oral contraceptives. The relative risk of venous thromboses is twice as high in obese women. If possible, oral contraceptives should be discontinued at least four weeks before elective surgery, as well as in the event of prolonged immobilisation. Contraceptives may be started again at the earliest two weeks after complete reambulation (also see section 4.4.1). If the tablets were not discontinued in time, thrombosis prophylaxis should be considered.

The risk of venous thromboembolic complications while using combined oral contraceptives is further increased:

– by increasing age
– by certain congenital / acquired thrombophilias (possibly signalled by a family history of venous thromboembolism in a sibling or parent relatively early in life)
– obesity (Body Mass Index $\geq$30 kg/m^2)
– in the first three to four weeks following delivery or a miscarriage in the second trimester (also see section 4.2.2). There is no consensus on the significance of varices and superficial phlebitis as related to the initial occurrence or progression of venous thrombosis.

Other diseases in which blood vessels may be involved include: systemic lupus erythematosus, haemolytic-uraemic syndrome, and chronic inflammatory intestinal diseases (Crohn's disease and ulcerative colitis).

The increased risk of thromboembolic events in the puerperium should be considered (see section 4.6 Pregnancy and lactation).

Symptoms of a venous or arterial thrombosis may include:

– unusual pain or swelling in one leg,
– sudden, severe chest pain, possibly radiating into the left arm,
– sudden difficulty in breathing,
– sudden cough,

– unusual, severe or persistent headache,
– sudden partial or complete loss of visual acuity,
– diplopia,
– slurred speech or aphasia,
– vertigo,
– collapse with or without seizure,
– sudden weakness or pronounced unilateral or focal numbness
– motor disturbances,
– acute abdomen.

4.4.3.2 Tumours

Breast
A meta-analysis of 54 epidemiological studies showed a slightly increased risk of breast cancer (RR 1.24) for women who are currently using combined oral contraceptives. This increased risk gradually returns to a baseline age-appropriate risk within 10 years following the discontinuation of combined oral contraceptives. Since breast cancer is rare in women under 40 years of age, the additional number of cases in current and recent users of combined oral contraceptives is small compared with the overall risk of breast cancer.

Cervix
Some epidemiological studies suggest that the long-term use of hormonal contraceptives in women infected with the human papilloma virus (HPV) represents a risk factor for the development of a cervical carcinoma. However, the extent to which these results are affected by other factors (e.g. differences in the number of sex partners or differences in the use of mechanical contraception methods) is not clear (See also section 4.4.4).

Liver
Benign liver adenomata have very rarely been reported in connection with the use of combined oral contraceptives. In isolated cases, they ruptured and led to life-threatening intra-abdominal bleeding. Should severe epigastric pain occur, a liver tumour, liver enlargement or intra-abdominal bleeding should be suspected.

Studies have shown an increased risk of hepatocellular carcinoma (HCC) in long-term users of combined oral contraceptives; however, this tumour is extremely rare in the absence of other pre-existing liver disease.

4.4.3.3 Other diseases

High blood pressure
There have been reports of an increase in blood pressure while using combined oral contraceptives, particularly in older women and with long-term use. Studies have showed that the frequency of high blood pressure increases with the progestogen content. Women with a history of hypertension or certain kidney diseases should use an alternative method of contraception (see sections 4.3, 4.4.1, 4.4.2).

Chloasma
Chloasma may occur, especially in women with a history of chloasma gravidarum. Women predisposed to chloasma should avoid exposure to the sun and ultraviolet radiation while taking combined oral contraceptives.

Hereditary angio-oedema
In women with hereditary angio-oedema, exogenously administered oestrogens may trigger or worsen symptoms.

Irregular bleeding
Breakthrough bleeding or spotting has been observed in users of combined oral contraceptives, especially in the first months of use. An accurate assessment of irregular bleeding is thus likely to be possible only after

about three months of use. The type and dose of the progestogen may be of importance. If bleeding irregularities persist or recur after previously regular cycles, then non-hormonal causes should be considered and, as is the case with any abnormal vaginal bleeding, adequate diagnostic measures are indicated to rule out malignancy or pregnancy. When both possibilities have been ruled out, the user may continue to take Zinnia P or change to another product. Intermenstrual bleeding may be an indication of reduced contraceptive efficacy (see sections 4.2 and 4.5).

The withdrawal bleed may not occur in some users during the seven-day period off tablets. If Zinnia P was not taken according to the instructions in section 4.2.1 prior to the first missed withdrawal bleed, or if the withdrawal bleed has been missed for two subsequent cycles, pregnancy must be ruled out before continuing use.

After discontinuing hormonal contraceptives, it may take some time to return to a normal cycle.

4.4.3.4 Reduced efficacy

The contraceptive efficacy of Zinnia P can be impaired:

– if tablets are forgotten (see section 4.2.4),
– through vomiting or diarrhoea (see section 4.2.5),
– if certain other medicinal products are taken at the same time (see section 4.5).

If combined oral contraceptives and St. John's wort are taken at the same time, an additional non-hormonal contraceptive method is recommended (see section 4.5).

4.4.4 Medical examination / consultation

Prior to the initial dose or resumption of taking combined oral contraceptives, a complete personal (and family) medical history should be taken and a thorough and complete medical examination conducted; they should be based on the contraindications (section 4.3) and warnings (section 4.4) and also regularly repeated throughout the use of combined oral contraceptives. The range and frequency of these checkups should be individually specified. In doing so, the following examinations should be conducted explicitly: measuring blood pressure, examining the breasts, the abdomen and the pelvic organs including cervical cytology, as well as determining relevant laboratory parameters.

Women should be informed that this product does not protect against HIV or other sexually transmitted infections. Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission.

Women who stop taking Zinnia P because they desire to have a child should be informed about the fact that folic acid deficiency can lead to neural tube defects in the unborn child and that periconceptional supplementation with folic acid is recommended. In addition to food rich in folic acid (vegetable, fruits, whole-grain products), 0.4 mg of folic acid should be taken daily. Ideally it should be taken four weeks prior to conception and continued up to week 12 of pregnancy. Any woman who has already been pregnant with a child having a neural tube defect should take 4 mg or 5 mg of folic acid daily for the same period. Consult the contraindications and warnings in the labelling of folic acid preparations.

4.4.5 Excipients

Zinnia P contains a small amount of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

Zinnia P contains a small amount of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency may experience symptoms of intolerance.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions of ethinylestradiol and levonorgestrel, the active substances in Zinnia P , with other medicinal products may increase or decrease the serum concentrations of the two sex steroids. Decreased serum concentrations of ethinylestradiol / levonorgestrel can result in an increase in breakthrough bleeding and menstrual cycle disturbances and lower the contraceptive efficacy of Zinnia P ; increased ethinylestradiol/ levonorgestrel serum levels can cause more frequent occurrence and intensified manifestations of adverse effects.

4.5.1 The following drugs may lower the serum concentration and reduce efficacy of the sex steroids contained in Zinnia P :

– all substances that increase gastrointestinal motility, e.g. metoclopramide,

– inducers of microsomal enzymes in the liver, especially rifampicin, also rifabutin, barbiturates, antiepileptic agents (such as barbiturates, barbexaclone, carbamazepine, phenytoin, primidone, oxcarbazepine, topiramate and felbamate), griseofulvin, modafinil, St. John's wort (Hypericum perforatum).

An additional non-hormonal method of contraception should be used for up to 28 days following the use of drugs that reduce the serum concentration of the sex steroids through an induction of hepatic microsomal enzymes. If the simultaneous administration of these inducing drugs extends beyond the last tablet in the current blister pack, the user should immediately start with the tablets in the next blister pack, without taking the placebo tablets in the current blister pack for 7 days, as would usually be the case.

If long-term therapy with microsomal enzyme-inducers is necessary, women should use non-hormonal contraception methods.

-HIV medications such as protease inhibitors (e.g ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine, efavirenz). These and other medications used in HIV disease may influence hepatic metabolism and reduce sex steroid levels. Combination oral contraceptives should not be used as the sole method of contraception in women taking HIV medications.

– certain antibiotics (e.g. ampicillin, tetracycline) in some women, possibly through a reduction in the enterohepatic circulation of oestrogens. In simultaneous therapy with antibiotics and Zinnia P , an additional non-hormonal contraception method should be used during treatment and for the first seven days following it.

4.5.2 The following drugs can increase the serum concentration of the sex steroids contained in Zinnia P :

– drugs that inhibit the sulphation of ethinylestradiol in the gastrointestinal wall, e.g. ascorbic acid or paracetamol (acetaminophen),
– atorvastatin (increases the AUC of ethinylestradiol by 20 %),
– drugs that inhibit microsomal enzymes in the liver, such as imidazole antifungal agents (e.g. fluconazole), indinavir and troleandomycin.

4.5.3 The sex steroids contained in Zinnia P can affect the metabolisation of other active substances

– by inhibiting hepatic-microsomal enzymes with the consequence of increased serum concentrations of active substances, such as diazepam (and several other benzodiazepines), cyclosporine, theophylline and glucocorticoids,

– through inducing hepatic glucuronidation with the consequence of decreased serum concentrations, for example, of clofibrate, paracetamol, morphine, lorazepam (as well as some other benzodiazepines) and lamotrigine.
The required amounts of insulin or oral antidiabetic agents may be altered
The prescribing information for any co-administered products should be examined for possible interactions with Zinnia P .

4.5.4 Laboratory tests

The results of some laboratory tests may be altered in women using combined oral contraceptives, including those assessing hepatic, adrenal and thyroid functions, plasma levels of carrier proteins (e.g. SHBG, lipoproteins), parameters for carbohydrate metabolism, coagulation and fibrinolysis. Type and extent depend in part on the dose of the administered hormones.

4.6. Pregnancy and lactation.

Zinnia P should not be used during pregnancy.
Pregnancy must be ruled out before starting to use the medicinal product. It should be immediately discontinued in the event of pregnancy.
Data from a limited number of exposed pregnancies show no unfavourable effects on the foetus with levonorgestrel alone.
Animal experimental studies have showed reproductive toxicity (see section 5.3).
Undesirable hormonal effects on the development of the urogenital tract cannot completely be ruled out.
Nevertheless most of the current epidemiological studies relevant to an unintentional exposure of the foetus to oestrogen / progestogen combinations did not show teratogenic or foetotoxic effects.

Zinnia P should not be used in the first 6 months of breast feeding, as milk production may be reduced and small quantities of the active substances may pass into the milk. Zinnia P may be used after 6 months of breast-feeding.

4.7 Effects on ability to drive and use machines

Zinnia P does not influence the ability to drive and use machines.

4.8. Undesirable effects

The most frequent adverse drug reactions (≥ 10%) related to the use of Zinnia P are headache (including migraine), spotting and intermenstrual bleeding.

The following adverse drug reactions have been observed following use of combined oral contraceptives containing ethinylestradiol / levonorgestrel:

Body system	Frequency of adverse reactions			
	Common ≥1% and <10%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%	Very rare <0.01%
Infections and infestations	Vaginitis, including candidiasis,			

Body system	Frequency of adverse reactions			
	Common ≥1% and <10%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%	Very rare <0.01%
Immune system disorders		Urticaria	Allergic reactions	Angio-oedema, severe anaphylactic reactions with respiratory and circulatory symptoms
Metabolic disturbances and trophopathy		Changes of appetite (increase or decrease)	Glucose intolerance	
Psychiatric disorders	Mood swings, including depression; changes of the libido			
Nervous system disorders	Nervousness; giddiness, dizziness			
Eye disorders	Visual disturbances		Contact lens intolerance	
Diseases of the gastrointestinal tract	Nausea, vomiting, abdominalgia	Diarrhoea, abdominal cramps, flatulence		
Diseases of the liver and the gall bladder			Cholestatic icterus	
Skin and subcutaneous tissue disorders	Acne	Skin rash, chloasma (melasma) possibly persisting, hirsutism, alopecia	Erythema nodosum Erythema multiforme	
Diseases of the genitals and mammary gland	Chest pain, sensitivity of the breasts, breast enlargement, mammary gland secretion, dysmenorrhea, changes in menstruation flow, changes in the cervical transformation zone and secretion, amenorrhea			
General diseases	Fluid retention / oedema			

Body system	Frequency of adverse reactions			
	Common ≥1% and <10%	Uncommon ≥0.1% and <1%	Rare ≥0.01% and <0.1%	Very rare <0.01%
Examinations	Weight changes (increase or decrease)	Increase in blood pressure, Changes of the serum lipid levels, including hyper-triglyceridaemia	Decrease in the serum folic acid levels	

See sections 4.4.3.1 and 4.4.3.2 with regard to further severe adverse reactions, such as thromboembolic diseases, liver tumours, cervical and breast cancer.

Moreover, the following adverse drug reactions have been reported in connection with the use of combined oral contraceptives. (The frequency of these reactions cannot be calculated from the reports.)

- optic neuritis (may cause partial or complete loss of vision),
– worsening of varicose veins,
- pancreatitis with a currently existing severe lipid metabolic disturbance,
– gall bladder disease, including gall stones (combined oral contraceptives can cause gall bladder disease or worsen existing gall bladder disease),
– haemolytic-uraemic syndrome,
– Herpes gestationis,
– otosclerosis,
– worsening of systemic lupus erythematosus,
– worsening of porphyria,
– worsening of Chorea minor (Sydenham's chorea),
– worsening of depression,
– worsening of chronic-inflammatory intestinal diseases (Crohn's disease and ulcerative colitis).

4.9 Overdose

Symptoms of an overdose with oral contraceptives in the case of adults and children may include: nausea, vomiting, chest tightness, giddiness, abdominal pain, sleepiness / tiredness; vaginal bleeding can occur in women and girls. There is no specific antidote. The treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations
ATC Code: G03AA07

Zinnia P , a combination product for oral contraception, contain ethinylestradiol (EE) and levonorgestrel (LNG).

The contraceptive effect of combination oral contraceptives is based on the interaction of various factors. The most important are the inhibition of ovulation and changes to cervical mucous.

5.2. Pharmacokinetic properties

Levonorgestrel

Absorption
Levonorgestrel is absorbed rapidly and completely following oral administration.

Following single dose administration of 2 tablets of Zinnia P in healthy volunteers, the mean (± SD) levonorgestrel C_{max} value was 9.7 (±3.6) ng/ml, the corresponding value for AUC was 145 (±91) ng.h/ml, and the mean levonorgestrel t_{max} value was 1.7 (±0.6) hours.

Distribution
Levonorgestrel is bound to serum albumin and sex-hormone binding globulin (SHBG). Only 1.1% of the total serum concentration of the active pharmaceutical substance is present as free steroid; 65 % is specifically bound to SHBG and about 35 % non-specifically to albumin. The rise of SHBG, induced by ethinylestradiol, affects the relative distribution of levonorgestrel in different protein fractions. The induction of the binding protein causes a rise of the SHBG-bound fraction and a decrease in the albumin-bound fraction. The apparent volume of distribution of levonorgestrel is 129 L following a single dose.

Metabolism
Levonorgestrel is primarily metabolised through reduction of the Δ4-3-oxo group and through hydroxylation at positions 2α, 1β and 16β and by subsequent conjugation. Most of the metabolites that circulate in blood are sulphates of 3α, 5β-tetrahydrolevonorgestrel, while excretion occurs predominantly in the form of glucuronides. Part of the unchanged levonorgestrel also circulates as 17β sulphate. Metabolic clearance can differ inter-individually by several fold, which may partially explain the broad fluctuations in levonorgestrel concentrations among users.

Elimination
The serum levels of levonorgestrel decrease in two phases. The terminal phase is characterised by a half-life of approximately 25 hours. Levonorgestrel and its metabolites are primarily eliminated in urine (40 - 68 %) and about 16 - 48 % in faeces.

Dynamic equilibrium (steady state)
Levonorgestrel levels in serum increase by about three-fold during continuous use, and attain dynamic equilibrium (steady state) during the second half of the treatment cycle. The pharmacokinetics of levonorgestrel are affected by the SHBG levels in serum, which rise by between 1.5 – 1.6 fold during the use of estradiol. This is why the clearance rate from serum and the distribution volume are slightly decreased (0.7 ml/min/kg or respectively about 100 L) with dynamic equilibrium (steady state).

Ethinylestradiol

Absorption
Ethinylestradiol is absorbed rapidly and completely following oral administration. Ethinylestradiol is exhaustively metabolised during absorption and first-pass hepatic metabolism, leading to a mean oral bioavailability of 45 % (inter-individual fluctuation is about 20 - 65 %).

Following single dose administration of 2 tablets of Zinnia P in healthy volunteers, the mean (± SD) ethinylestradiol C_{max} value was 152 (±49) pg/ml, the corresponding value for AUC was 1076 (±504) pg.h/ml, and the mean ethinylestradiol t_{max} value was 1.7 (±0.3) hours.

Distribution

Ethinylestradiol is highly (approximately 98%) but non-specifically bound to serum albumin, and induces an increase in the serum concentrations of SHBG. The apparent volume of distribution of ethinylestradiol is 2.8–8.6 L/kg.

Metabolism
Ethinylestradiol is metabolised by presystemic conjugation in the small intestine mucosa and in the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation, during which a wide variety of hydroxylated and methylated metabolites are formed. These can be detected in serum as free metabolites or as glucuronide or sulphate conjugates. Ethinylestradiol is subject to an enterohepatic cycle.

Elimination
The serum levels of ethinylestradiol decrease in two phases, which are characterised by half-lives of approximately 1 hour and 10 to 20 hours, respectively. Ethinylestradiol is not eliminated in its unchanged form. The metabolites are eliminated via urine and bile in a ratio of 4 to 6.

Dynamic equilibrium (steady state)
The ethinylestradiol serum concentration almost doubles following continuous use. Due to daily use and the variable half-life in the terminal phase of serum clearance, dynamic equilibrium (steady state) is reached after approximately one week.

5.3. Preclinical safety data

The toxicity profiles of ethinylestradiol and levonorgestrel are well known.

Because of the pronounced differences in species, results from animal experimental testing with oestrogens possess limited predictive value for administration to humans.

In experimental animals, ethinylestradiol exhibits an embryo-lethal effect in relatively small dosage; malformations of the urogenital system and feminization of male foetuses have been observed. Levonorgestrel showed an embryo-lethal effect in animal experiments and, in high doses, a virilizing effect on female foetuses. Reproduction-toxicological studies in rats, mice and rabbits did not furnish any indication of a teratogenic effect.

Preclinical data for ethinylestradiol and levonorgestrel from conventional studies on chronic toxicity, genotoxicity and on carcinogenic potential do not show relevant risks for humans beyond those already described.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Active tablets
Tablet core: Lactose monohydrate, magnesium stearate, maize starch, povidone, talc

Tablet coating: Calcium carbonate, carnauba wax, glycerol, macrogol, povidone, sucrose talc, titanium dioxide

Placebo tablets
Tablet core: Lactose, magnesium stearate, maize starch, povidone, talc

Tablet coating: Calcium carbonate, carnauba wax, glycerol, macrogol, povidone, sucrose, talc, titanium dioxide, yellow oxide of iron

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store below 30°C. Store in the original package. Protect from light.

6.5 Nature and contents of container

Zinnia P tablets are provided in clear transparent PVC/PVdC-Alu blister cards in a carton, containing 1, 3, 6 or 100 blister cards of 28 tablets each.

6.6 Special precautions for disposal

No special requirements. Any unused product should be disposed of in accordance with local requirements.

7. SUPPLIER

Mylan Laboratories Limited
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Hyderabad, Telangana – 500033, India

8. WHO REFERENCE NUMBER (PREQUALIFICATION NUMBER)

RH 035

9. DATE OF FIRST PREQUALIFICATION/RENEWAL OF PREQUALIFICATION

21 October 2013

10. DATE OF REVISION OF THE TEXT

December 2014. Section 7 updated in February 2017.
Section 6.3 updated in May 2021.

References

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http://www.who.int/reproductivehealth/publications/family_planning/provider_brief_hc_liver_disease.pdf

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

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