Zinnia-F

Levonorgestrel and Ethinylestradiol Tablets with Ferrous Fumarate Tablets BP

28 Tablets

Composition

Each Sugar Coated white Tablet contains

Levonorgestrel Ph.Eur. 150 mcg
Ethinylestradiol Ph.Eur. 30 mcg

Each Sugar Coated brown Tablet contains

Ferrous Fumarate BP 75 mg
(equivalent to 24.375 mg of Ferrous Iron)

Description

Zinnia-F provides a dosage regimen consisting of 21 white progestogen-estrogens contraceptive tablets and 7 brown Ferrous Fumarate (placebo) tablets.

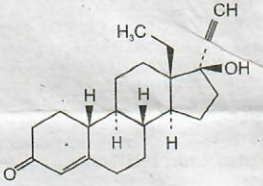
Each white tablet contains 150 mcg Levonorgestrel Ph.Eur. and 30 mcg Ethinylestradiol Ph.Eur.

Each white tablet also contains the following inactive ingredients: Lactose Monohydrate, Talc, Magnesium stearate, Maize Starch, Povidone K25, Povidone K-90, Glycerol, Sucrose, Calcium Carbonate, Macrogol 6000, Titanium dioxide, Purified water and Carnauba wax.

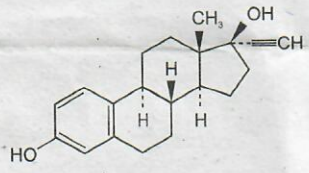
Each brown tablet contains Ferrous Fumarate, Starch Maize, Polysorbate 80, Methyl paraben, Propyl paraben, Sodium Starch Glycolate, Purified Talc, Magnesium Stearate, Shellac, Isopropyl Alcohol, Sodium Benzoate, Gum Acacia, Sucrose, Red Oxide of Iron, Titanium Dioxide, Carnauba Wax, Purified water and Chloroform.

The Ferrous Fumarate tablets do not serve any therapeutic purpose.

The structural formulas for the active hormones are:



13-ethyl-17-hydroxy-18, 19-dinor-17-pregn-4-en-20- yn-3-one



19-nor-17-pregna-1, 3, 5 (10)-trien-20-yne-3, 17-diol

PHARMACEUTICAL FORM

Sugar-coated tablets

CLINICAL PARTICULARS

Therapeutic indications

Oral contraception and the recognised gynaecological indications for such oestrogen-progestogen combinations.

Posology and method of administration

First treatment cycle: 1 tablet daily for 28 days, starting on the first day of the menstrual cycle. 21 active tablets are taken followed by 7 Ferrous Fumarate (placebo) tablets. Contraceptive protection begins immediately.

Subsequent cycles: Tablet-taking is continuous, which means that the next pack of Zinnia-F follows immediately without a break. A withdrawal bleed usually occurs when the Ferrous Fumarate tablets are being taken.

Changing from 21-day combined oral contraceptives: The first tablet of Zinnia-F should be taken on the first day immediately after the end of the previous oral contraceptive course. Additional contraceptive precautions are not required.

Changing from a combined Every Day pill (28 -day pill): Zinnia-F should be started after taking the last active tablet from the previous Every Day pill pack. The first Zinnia-F tablet is taken the next day. Additional contraceptive precautions are not then required.

Changing from a progestogen-only pill (POP): The first tablet of Zinnia-F should be taken on the first day of bleeding, even if a POP has already been taken on that day. Additional contraceptive precautions are not then required. The remaining progestogen-only pills should be discarded.

Post-partum and post-abortum use: After pregnancy, oral contraception can be started 21 days after a vaginal delivery, provided that the patient is fully ambulant and there are no puerperal complications. Additional contraceptive precautions will be required for the first 7 days of tablet taking to ensure adequate contraceptive cover if early ovulation has occurred. Since the first post-partum ovulation may precede the first bleeding, another method of contraception should be used in the interval between childbirth and the first course of tablets. After a first-trimester abortion, oral contraception may be started immediately in which case no additional contraceptive precautions are required.

Special circumstances requiring additional contraception

Incorrect administration: Errors in taking the 7 Ferrous Fumarate (Placebo) tablets (i.e. the brown tablets in the last row) can be ignored.

A single delayed active tablet should be taken as soon as possible, and if this can be done within 12 hours of the correct time, contraceptive protection is maintained.

With longer delays in taking active tablets, additional contraception is needed. Only the most recently delayed tablet should be taken, earlier missed tablets being omitted, and additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used for the next 7 days, while the next 7 active tablets are being taken. Therefore, if the 7 days additional contraception extend beyond the last active tablet, the user should finish taking all the active tablets, discard the Ferrous Fumarate (Placebo) tablets and start a new pack of Zinnia-F the next day with an appropriate active tablet. Thus, active tablet follows active tablet with no 7 day break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. Some breakthrough bleeding may occur on tablet taking days but this is not clinically significant. If the patient does not have a withdrawal bleed following the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack.

Gastro-intestinal upset: Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. Tablet-taking from the current pack should be continued. Additional non-hormonal methods of contraception (except the rhythm or temperature methods) should be used during the gastro-intestinal upset and for 7 days following the upset. If these 7 days extend beyond the last active tablet the user should finish taking all the active tablets, discard the Ferrous Fumarate (Placebo) tablets and start a new pack of Zinnia-F the next day with an appropriate active tablet. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before starting the next pack. Other methods of contraception should be considered if the gastro-intestinal disorder is likely to be prolonged.

Children and the elderly: Zinnia-F is an oral contraceptive and is not applicable in children or the elderly.

Contraindications

1. Pregnancy
2. Severe disturbances of liver function, jaundice or persistent itching during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome, previous or existing liver tumours
3. Existing or a history of confirmed venous thromboembolism (VTE), family history of idiopathic VTE and other known risk factors for VTE.

4. Existing or previous arterial thrombotic or embolic processes.
5. Conditions which predispose to thromboembolism e.g. disorders of the clotting processes, valvular heart disease and atrial fibrillation
6. Sickle-cell anaemia
7. Mammary or endometrial carcinoma, or a history of these conditions
8. Severe diabetes mellitus with vascular changes
9. Disorders of lipid metabolism
10. History of herpes gestationis
11. Deterioration of otosclerosis during pregnancy
12. Undiagnosed abnormal vaginal bleeding
13. Hypersensitivity to any of the components of Zinnia-F.

Special warnings and precautions for use

Warnings:

The use of any combined oral contraceptive 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 cases per 100 000 pregnancies. Some epidemiological studies have reported a greater risk of VTE for women using combined oral contraceptives containing desogestrel or gestodene (the so-called 'third generation' pills) than for women using pills containing levonorgestrel (the so-called 'second generation' pills).

The spontaneous incidence of VTE in healthy non-pregnant women (not taking any oral contraceptive) is about 5 cases per 100,000 per year. The incidence in users of second generation pills is about 15 per 100,000 women per year of use. The incidence in users of third generation pills is about 25 cases per 100,000 women per year of use; this excess incidence has not been satisfactorily explained by bias or confounding. The level of all these risks of VTE increases with age and is likely to be further increased in women with other known risk factors for VTE such as obesity.

The risk of venous and/or arterial thrombosis associated with combined oral contraceptives increases with:

- age
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- a positive family history (i.e. venous or arterial 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 COC use
- obesity (body mass index over 30 kg/m^2)
- dyslipoproteinaemia
- hypertension
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least six weeks in advance) and not to resume until two weeks after complete remobilisation.
- There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.
- The increased risk of thromboembolism in the puerperium must be considered.
- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome., chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), sickle cell disease and subarachnoid haemorrhage.
- 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 the COC.
- Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. The evidence is clear that combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer.

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some studies, but there continues to be controversy about the extent to which this is attributable to the confounding effects of sexual behaviour and other factors.

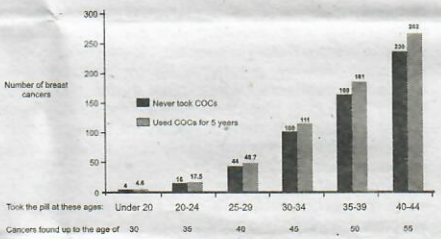
A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives (COCs). The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

Breast cancer is rare among women under 40 years of age whether or not they take COCs. Whilst this background risk increases with 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 (see bar chart)

The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

The possible increase in risk of breast cancer should be discussed with the user and weighed against the benefits of COCs taking into account the evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

Estimated cumulative numbers of breast cancers per 10,000 women diagnosed in 5 years of use and up to 10 years after stopping COCs, compared with numbers of breast cancers diagnosed in 10,000 women who had never used COCs



The possibility cannot be ruled out that certain chronic diseases may occasionally deteriorate during the use of combined oral contraceptives.

In rare cases benign and, in even rarer cases, malignant liver tumours leading in isolated cases to life-threatening

intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Zinnia-F. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis.

Reasons for stopping oral contraception immediately:

1. Occurrence for the first time, or exacerbation, of migrainous headaches or unusually frequent or unusually severe headaches
2. Sudden disturbances of vision or hearing or other perceptual disorders
3. First signs of thrombophlebitis or thromboembolic symptoms (e.g. unusual pains in or swelling of the leg(s), stabbing pains on breathing or coughing for no apparent reason). Feeling of pain and tightness in the chest
4. Six weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. Do not restart until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin
5. Onset of jaundice, hepatitis, itching of the whole body
6. Increase in epileptic seizures
7. Significant rise in blood pressure
8. Onset of severe depression
9. Severe upper abdominal pain or liver enlargement
10. Clear exacerbation of conditions known to be capable of deteriorating during oral contraception or pregnancy
11. Pregnancy is a reason for stopping immediately because it has been suggested by some investigations that oral contraceptives taken in early pregnancy may slightly increase the risk of foetal malformations. Other investigations have failed to support these findings. The possibility therefore cannot be excluded, but it is certain that if a risk exists at all, it is very small.

Precautions:
Assessment of women prior to starting oral contraceptives (and at regular intervals thereafter) should include a personal and family medical history of each woman. Physical examination should be guided by this and by the contraindications and warnings for this product. The frequency and nature of these assessments should be based upon relevant guidelines and should be adapted to the individual woman, but should include measurement of blood pressure and, if judged appropriate by the clinician, breast, abdominal and pelvic examination including cervical cytology.

The following conditions require strict medical supervision during medication with oral contraceptives. Deterioration or first appearance of any of these conditions may indicate that use of the oral contraceptive should be discontinued:

Diabetes mellitus, or a tendency towards diabetes mellitus (e.g. unexplained glycosuria), hypertension, varicose veins, a history of phlebitis, otosclerosis, multiple sclerosis, epilepsy, porphyria, tetany, disturbed liver function, Sydenham's chorea, renal dysfunction, family history of clotting disorders, obesity, family history of breast cancer and patient history of benign breast disease, history of clinical depression, systemic lupus erythematosus, uterine fibroids and migraine, gall-stones, cardiovascular diseases, chloasma, asthma, an intolerance of contact lenses, or any disease that is prone to worsen during pregnancy.

Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of oral contraceptives, especially when these conditions existed prior to use. Women should be informed of this possibility.

Interaction with other medicinal products and other forms of interaction
Hepatic enzyme inducers such as barbiturates, primidone, phenobarbitone, phenytoin, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the efficacy of Zinnia-F. For women receiving long-term therapy with hepatic enzyme inducers, another method of contraception should be used. The use of ampicillin and other antibiotics may also reduce the efficacy of Zinnia-F, possibly by altering the intestinal flora.

Women receiving short courses of enzyme inducers or broad spectrum antibiotics should take additional, non-hormonal (except rhythm or temperature method) contraceptive precautions during the time of concurrent medication and for 7 days afterwards. If these 7 days extend beyond the last active tablet the user should finish taking all the active tablets, discard the Ferrous Fumarate (Placebo) tablets and start a new pack of Zinnia-F the next day with an appropriate active tablet. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment stops, even if only a short course was administered.

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

The herbal remedy St John's wort (Hypericum perforatum) should not be taken concomitantly with Zinnia-F as this could potentially lead to a loss of contraceptive effect.

Pregnancy and lactation
Zinnia-F is not indicated during pregnancy. If pregnancy occurs during treatment with Zinnia-F, further intake must be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

The use of Zinnia-F during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances are excreted with the milk. Mothers who are breast-feeding may be advised instead to use another method of contraception.

Effects on ability to drive and use machines
None known.

Undesirable effects
In rare cases, headaches, gastric upsets, nausea, vomiting, breast tenderness, changes in body weight, changes in libido, depressive moods can occur.

In predisposed women, use of Zinnia-F can sometimes cause chloasma which is exacerbated by exposure to sunlight. Such women should avoid prolonged exposure to sunlight.

Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

Menstrual changes:
1. Reduction of menstrual flow: This is not abnormal and it is to be expected in some patients. Indeed, it may be beneficial where heavy periods were previously experienced.

2. Missed menstruation: Occasionally, withdrawal bleeding may not occur at all. If the tablets have been taken correctly, pregnancy is very unlikely. If withdrawal bleeding fails to occur at the end of a second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

Intermenstrual bleeding: 'Spotting' or heavier 'breakthrough bleeding' sometimes occur during tablet taking, especially in the first few cycles, and normally cease spontaneously. Zinnia-F should therefore, be continued even if irregular bleeding occurs. If irregular bleeding is persistent, appropriate diagnostic measures to exclude an organic cause are indicated and may include curettage. This also applies in the case of spotting

which occurs at irregular intervals in several consecutive cycles or which occurs for the first time after long use of Zinnia-F.

Effect on blood chemistry: The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

Overdose
Overdosage may cause nausea, vomiting and, in females, withdrawal bleeding.

There are no specific antidotes and treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Zinnia-F is an oestrogen-progestogen combination which acts by inhibiting ovulation by suppression of the mid-cycle surge of luteinizing hormone, the inspissation of cervical mucus so as to constitute a barrier to sperm, and the rendering of the endometrium unreceptive to implantation.

Pharmacokinetic properties
Levonorgestrel
Levonorgestrel is absorbed quickly and completely. Maximum active substance levels of approx. 3 ng/ml were reached in serum just one hour after ingestion of Zinnia-F. The serum concentrations subsequently fell in 2 phases with half-lives of around 0.5 hours and 20 hours. The metabolic clearance rate from plasma is approx. 1.5 ml/min/kg.

Levonorgestrel is eliminated not in unchanged form, but in the form of metabolites with a half-life of around one day and in almost equal proportions via the kidney and bile. Biotransformation takes place via the familiar pathways of steroid metabolism. There are no known pharmacologically active products of metabolism.

Levonorgestrel is bound to serum albumin and SHBG. Only around 1.5% of the respective total concentration is present in unbound form, while approx. 65% is bound to SHBG. The relative proportions (free, albumin-bound, SHBG-bound) depend on the concentration of SHBG. After induction of the binding protein, the portion bound to SHBG increases, while the free portion and that bound to albumin decreases.

After daily repeated ingestion, levonorgestrel accumulates by about the factor 2. A steady state is reached during the second half of the treatment cycle. The pharmacokinetics of levonorgestrel are dependent on the concentration of SHBG in plasma. Under treatment with Zinnia-F, an increase in the serum levels of SHBG effect a concomitant increase in the specific binding capacity and therefore also an increase in levonorgestrel serum levels.

The levonorgestrel serum levels do not change any further after 1 - 3 cycles of use owing to the fact that SHBG induction is concluded. Compared to a single administration, 3 - 4 fold higher levonorgestrel serum levels are reached in the steady state.

The absolute bioavailability of levonorgestrel amounts to almost 100%.

Approx. 0.1% of the maternal dose can be passed on to a baby with the breast milk.

Ethinylestradiol

Orally administered ethinylestradiol is absorbed quickly and completely. Ingestion of Zinnia-F leads to maximum plasma levels of approx. 100 pg/ml after 1 - 2 hours. The substance concentration then falls in 2 phases for which half-lives of around 1 - 2 hours and about 20 hours have been determined. For technical reasons, these data can only be calculated at higher dosages.

An imaginary distribution volume of around 5 l/kg and a metabolic clearance rate from plasma of approx. 5 ml/min/kg have been determined for ethinylestradiol.

Ethinylestradiol is bound non-specifically to serum albumin to the extent of 98%.

Ethinylestradiol is metabolised even during its absorption phase and during its first liver transit, leading to reduced and individually varying oral bioavailability. Ethinylestradiol is eliminated not in unchanged form, but in the form of metabolites with a half-life of around one day. The excretion ratio is 40 (urine) : 60 (bile).

Because of the half-life of the terminal elimination phase from plasma, a steady state characterised by a 30 - 40% higher plasma substance level becomes established after approx. 5 - 6 daily administrations.

The absolute bioavailability of ethinylestradiol is subject to considerable interindividual variations. After oral ingestion, it amounts to around 40 - 60% of the dose.

In women with fully established lactation, around 0.02% of the maternal dose can be passed on to the baby with the breast milk.

Other drugs can have a negative or positive effect on the systemic availability of ethinylestradiol. No interaction with vitamin C takes place. On continuous use, ethinylestradiol induces the hepatic synthesis of CBG and SHBG, the extent of SHBG induction being dependent on the type and dose of the simultaneously administered progestogen.

Preclinical safety data
There is no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

Shelf life
3 years

Special precautions for storage
Store below 30°C
Keep out of reach of children

Presentation
Blister pack of 28 tablets

Manufactured by:
Jai Pharma Ltd., INDIA

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