HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NATAZIA safely and effectively. See full prescribing information for NATAZIA.

NATAZIA (estradiol valerate and estradiol valerate/dienogest) tablets, for oral use

Initial U.S. Approval: 2010

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Women over 35 years old who smoke should not use Natazia. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Heavy Menstrual Bleeding (1.2)	3/2012
Warnings and Precautions, Thromboembolic Disorders (5.1)	2/2012

----------INDICATIONS AND USAGE----------

- Natazia is an estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1) The efficacy of Natazia in women with a body mass index (BMI) of >30 kg/m^2 has not been evaluated. (1, 8.8)
- Treatment of heavy menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)
- Do not skip or delay intake by more than 12 hours. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Natazia consists of 28 film-coated, unscored tablets in the following order (3):

- 2 dark yellow tablets each containing 3 mg estradiol valerate
- 5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest
- 17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest
- 2 dark red tablets each containing 1 mg estradiol valerate
- 2 white tablets (inert)

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

----------WARNINGS AND PRECAUTIONS----------

- Vascular risks: Stop Natazia if a thrombotic event occurs. Stop Natazia at least 4 weeks before and through 2 weeks after major surgery. Start Natazia no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Natazia if jaundice occurs. (5.3)
- High blood pressure: Do not prescribe Natazia for women with uncontrolled hypertension or hypertension with vascular disease. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Natazia. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Natazia if indicated. (5.7)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.8)
- CYP3A4 induction: Women taking strong CYP3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive due to the possibility of decreased contraceptive efficacy. (5.13, 7.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 2%) in clinical trials for Natazia are headache (including migraines) 13%, breast pain 7%, menstrual disorders 7%, nausea or vomiting 6%, acne 4%, mood changes 3% and increased weight 3%. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Not recommended; can decrease milk production. (8.3)
- Body Mass Index: The safety and efficacy of Natazia in women with a body mass index (BMI) of >30 kg/m^2 has not been evaluated. (8.8)

See 17 **for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

Revised: 03/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *[See Contraindications (4).]*

1 INDICATIONS AND USAGE

1.1 Oral Contraception

Natazia® is indicated for use by women to prevent pregnancy.

The efficacy of Natazia in women with a body mass index (BMI) of > 30 kg/m^2 has not been evaluated.

1.2 Heavy Menstrual Bleeding

Natazia is also indicated for the treatment of heavy menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception *[see Clinical Studies (*14.2*)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Natazia

To achieve maximum contraceptive effectiveness, Natazia must be taken exactly as directed. Take one tablet by mouth at the same time every day. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or intake delayed by more than 12 hours. For patient instructions for missed pills, see FDA-Approved Patient Labeling.

2.2 How to Start Natazia

Instruct the patient to begin taking Natazia on Day 1 of her menstrual cycle (that is, the first day of her menstrual bleeding). See FDA-Approved Patient Labeling. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 9 days.

For postpartum women who do not breastfeed or after a second trimester abortion, start Natazia no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Natazia postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Natazia for 9 consecutive days. The possibility of ovulation and conception prior to initiation of medication should also be considered.

If the patient is switching from a combination hormonal method such as:

- Another pill
- Vaginal ring
- Patch

- Instruct her to take the first dark yellow pill on the first day of her withdrawal bleed. She should not continue taking the pills from her previous birth control pack. If she does not have a withdrawal bleed, rule out pregnancy before starting Natazia.
- If she previously used a vaginal ring or transdermal patch, she should start using Natazia on the day the ring or patch is removed.
- Instruct the patient to use a non-hormonal back-up method such as a condom or spermicide for the first 9 days.

If the patient is switching from a progestin-only method such as a:

- Progestin-only pill
- Implant
- Intrauterine system
- Injection

- Instruct her to take the first dark yellow pill on the day she would have taken her next progestin-only pill or on the day of removal of her implant or intrauterine system or on the day when she would have had her next injection.
- Instruct the patient to use a non-hormonal back-up method such as a condom or spermicide for the first 9 days.

2.3 Advice in case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3-4 hours after taking a colored tablet, this can be regarded as a missed tablet.

3 DOSAGE FORMS AND STRENGTHS

Natazia (estradiol valerate and estradiol valerate/dienogest) tablets are available in blister packs.

Each blister pack contains 28 round, biconvex, film-coated tablets in the following order:

- 2 dark yellow tablets, with an embossed "DD" in a regular hexagon on one side, each containing 3 mg estradiol valerate
- 5 medium red tablets, with an embossed "DJ" in a regular hexagon on one side, each containing 2 mg estradiol valerate and 2 mg dienogest
- 17 light yellow tablets, with an embossed "DH" in a regular hexagon on one side, each containing 2 mg estradiol valerate and 3 mg dienogest
- 2 dark red tablets, with an embossed "DN" in a regular hexagon on one side, each containing 1 mg estradiol valerate
- 2 white tablets (inert), with an embossed "DT" in a regular hexagon on one side

4 CONTRAINDICATIONS

Do not prescribe Natazia to women who are known to have the following:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (*5.1*)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (*5.1*)]*
  - Have coronary artery disease *[see Warnings and Precautions (*5.1*)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (*5.1*)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (*5.1*)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (*5.4*)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (*5.6*)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (*5.7*)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (*5.2*)]*

- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.3), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Natazia if an arterial or venous thrombotic event (VTE) occurs.

The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of VTE in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Natazia at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Natazia no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Natazia if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. *[See Adverse Reactions (6).]*

5.2 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Natazia because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

Endometrial biopsies performed in a subset of subjects in a Phase 3 Natazia clinical trial did not reveal any unexpected or concerning findings for subjects taking COCs. *[See Adverse Reactions (6.1).]*

5.3 Liver Disease

Discontinue Natazia if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.4 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Natazia if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Natazia. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking Natazia develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Natazia if indicated.

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.

5.8 Bleeding Irregularities

Breakthrough bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Women who are not pregnant and use Natazia, may experience amenorrhea. Based on patient diaries, amenorrhea occurs in approximately 16% of cycles in women using Natazia. Pregnancy should be ruled out in the event of amenorrhea occurring in two or more consecutive cycles. Some women may encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

Based on patient diaries from three clinical trials evaluating the safety and efficacy of Natazia for contraception, 10-23% of women experienced intracyclic bleeding per cycle.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. Oral contraceptive use should be discontinued if pregnancy is confirmed.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Women with a history of depression should be carefully observed and Natazia discontinued if depression recurs to a serious degree.

5.11 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs *[see Drug Interactions (7.2)]*.

5.12 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.13 Drug Interactions

Women who take medications that are strong cytochrome P450 3A4 (CYP3A4) inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive while using these inducers and for at least 28 days after discontinuation of these inducers due to the possibility of decreased contraceptive efficacy. *[See Drug Interactions (7.1) and Clinical Pharmacology (12.3).]*

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. 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 while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (*5.1*)]*
- Liver disease *[see Warnings and Precautions (*5.3*)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Contraception and Heavy Menstrual Bleeding Studies

A total of 2,131 women, 18 to 54 years of age, who took at least one dose of Natazia were enrolled in four clinical phase 3 trials. A total of 1,867 subjects were included in two clinical phase 3 studies with a treatment duration up to 28 cycles with Natazia as an oral contraceptive and 264 subjects in the two phase 3 clinical trials with a treatment duration of 7 cycles evaluating Natazia in the treatment of heavy, prolonged, and/or frequent menstrual bleeding in women without organic pathology. *[See Clinical Studies (14.1, 14.2.)]*

Adverse Reactions Leading to Study Discontinuation: 11.4% of the women discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were menstrual disorder (metrorrhagia, menorrhagia, menstruation irregular, genital hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding) (2.3%); mood changes (depression, mood swings, mood altered, depressed mood, dysthymic disorder, crying) (1.2%); acne (1.1%), headache (including migraines) (1.1%), and weight increased (0.7 %).

Common Adverse Reactions (≥ 2%): headache (including migraines) (12.7%), breast pain, discomfort or tenderness (7.0%), menstrual disorders (metrorrhagia, menstruation irregular, menorrhagia, vaginal hemorrhage, dysfunctional uterine bleeding, genital hemorrhage, abnormal withdrawal bleeding, uterine hemorrhage) (6.9%), nausea or vomiting (6.0%), acne (3.9%), mood changes (depression, mood swings, depressed mood, mood altered, affect lability, dysthymic disorder, crying) (3.0%) and increased weight (2.9%).

Serious Adverse Reactions: myocardial infarction (2 cases), ruptured ovarian cyst (2 cases), deep vein thrombosis, focal nodular hyperplasia of the liver, uterine leiomyoma, acute cholecystitis, and chronic acalculous cholecystitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Natazia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, myocardial infarction and stroke), hypertension

Hepatobiliary disorders: Gallbladder disease, hepatitis

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Fluid retention, hypertriglyceridemia

Nervous system disorders: Dizziness

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme

Gastrointestinal disorders: Gastrointestinal symptoms (for example, abdominal pain)

Infections and infestations: Vulvovaginal candidiasis

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

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 or were studied in clinical trials with Natazia.

***CYP3A4 Inducers*:** Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include barbiturates, bosentan, felbamate, griseofulvin, oxcarbazepine, and topiramate. Counsel women to use an alternative method of contraception or a back-up method when moderate or weak enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Dienogest is a substrate of CYP3A4. Women who take medications that are strong CYP3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive while using these inducers and for at least 28 days after discontinuation of these inducers due to the possibility of decreased contraceptive efficacy.

The effect of the CYP3A4 inducer rifampicin was studied in healthy postmenopausal women. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to a 52 % and 83% decrease in the mean C_{max} and AUC (0–24hr), respectively, for dienogest and a 25% and 44% decrease in C_{max} and AUC (0–24hr), respectively, for estradiol at steady state.

Strong CYP3A4 Inhibitors: Strong CYP3A4 inhibitors such as ketoconazole increased hormone serum concentrations. In a study investigating the effect of ketoconazole on dienogest and estradiol pharmacokinetics, co-administration with the strong CYP3A4 inhibitor ketoconazole resulted in a 186% increase of AUC (0–24hr) at steady state for dienogest and a

57% increase for estradiol. There was also a 94% and 65% increase of C_{max} at steady state for dienogest and estradiol when co-administered with ketoconazole.

Moderate CYP3A4 Inhibitors: The AUC (0–24hr) of dienogest and estradiol at steady state were increased by 62% and 33%, respectively, when co-administered with a moderate CYP3A4 inhibitor, erythromycin. There was also a 33% and 51% increase of Cmax at steady state for dienogest and estradiol, respectively, when co-administered with erythromycin.

Other known CYP3A4 inhibitors like azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants, and grapefruit juice may increase plasma concentrations of dienogest.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors: Significant changes (increase and decrease) in plasma concentrations of estrogen and progestin have been noted in some cases of co-administration of HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro studies with human CYP enzymes did not indicate an inhibitory potential of dienogest at clinically relevant concentrations.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins *[see Warnings and Precautions (5.11) and Drug Interactions (7.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Natazia have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Natazia has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

The pharmacokinetics of Natazia has not been studied in subjects with renal impairment, but an effect requiring dose adjustment is unlikely to be present.

8.7 Patients with Hepatic Impairment

The pharmacokinetics of Natazia has not been studied in subjects with hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. *[See Contraindications (4) and Warnings and Precautions (5.3).]*

8.8 Body Mass Index

The safety and efficacy of Natazia in women with a BMI of > 30 kg/m^2 has not been evaluated.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

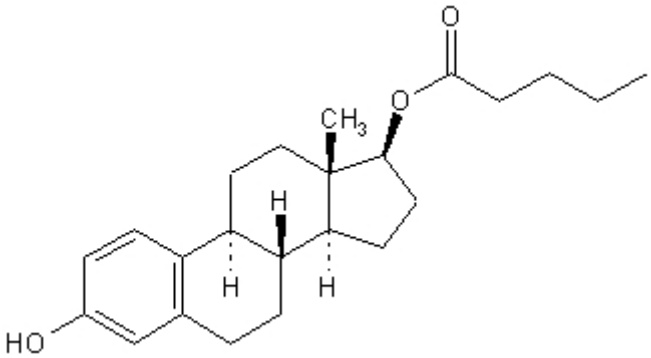
11 DESCRIPTION

Natazia (estradiol valerate and estradiol valerate/dienogest) tablets provide an oral contraceptive regimen consisting of 26 active film-coated tablets that contain the active ingredients specified for each tablet below, followed by two inert film-coated tablets:

- 2 dark yellow tablets each containing 3 mg estradiol valerate
- 5 medium red tablets each containing 2 mg estradiol valerate and 2 mg dienogest
- 17 light yellow tablets each containing 2 mg estradiol valerate and 3 mg dienogest
- 2 dark red tablets each containing 1 mg estradiol valerate
- 2 white tablets (inert)

Natazia also contains the excipients lactose monohydrate, maize starch, maize starch pre-gelatinized, povidone 25, magnesium stearate, hypromellose, macrogol 6000, talc, titanium dioxide, and ferric oxide pigment, yellow, or ferric oxide pigment, red.

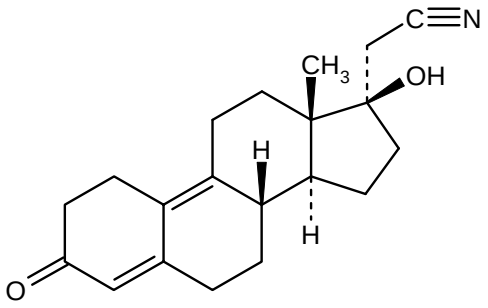
The empirical formula of estradiol valerate is $C_{23}H_{32}O_3$ and the chemical structure is:



Estradiol Valerate

The chemical name of estradiol valerate is Estra-1,3,5(10)-triene-3,17-diol(17ß)-,17-pentanoate.

The empirical formula of dienogest is C_{20} H_{25} NO_2 and the chemical structure is:



Dienogest

The chemical name of dienogest is (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

The estrogen in Natazia is estradiol valerate, a synthetic prodrug of 17ß-estradiol. The progestin in Natazia is dienogest (DNG). DNG displays properties of 19-nortestosterone derivatives as well as properties associated with progesterone derivatives. *[See Nonclinical Toxicology (13.2).]*

Cardiac Electrophysiology

The effect of Natazia on QT prolongation was evaluated in a randomized, double-blind, positive (moxifloxacin 400 mg) and negative (placebo) controlled crossover study in healthy subjects. A total of 53 subjects were administered Natazia (containing 3 mg dienogest and 2 mg estradiol valerate), dienogest 10 mg, and placebo as once daily doses for 4 days, and moxifloxacin 400 mg as a single oral dose. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 msec, the threshold for regulatory concern.

12.3 Pharmacokinetics

Absorption

After oral administration of estradiol valerate, cleavage to 17β-estradiol and valeric acid takes place during absorption by the intestinal mucosa or in the course of the first liver passage. This gives rise to estradiol and its metabolites, estrone and other metabolites. Maximum serum estradiol concentrations of 73.3 pg/mL are reached at a median of approximately 6 hours (range: 1.5–12 hours) and the area under the estradiol concentration curve [AUC(0–24hr)] was 1301 pg·hr/mL after single ingestion of a tablet containing 3 mg estradiol valerate under fasted condition on Day 1 of the 28-day sequential regimen.

Bioavailability of dienogest is about 91%. Maximum serum dienogest concentrations of 91.7 ng/mL are reached at a median of approximately 1 hour (range: 0.5–1.5 hour) and the area under the dienogest concentration curve [AUC(0–24hr)] was 964 ng/mL after single oral administration of Natazia tablet containing 2 mg estradiol valerate/3 mg dienogest under fasted condition. The pharmacokinetics of dienogest are dose-proportional within the dose range of 1–8 mg. Steady state is reached after 4 days of the same dosage of 2 mg dienogest. The mean accumulation ratio for AUC (0–24hr) is approximately 1.24.

The mean plasma pharmacokinetic parameters at steady state following repeated oral doses of a 2 mg estradiol valerate/3 mg dienogest combination tablet in fertile women under fasted condition are reported in Table 1.

Table 1: **Arithmetic Mean (SD) Serum Pharmacokinetic Parameters at Steady-state (on Day 24) following Repeated Oral Doses of 2 mg EV/3 mg DNG on Days 8–24 of the 28 day Regimen in Fertile Women under Fasted Condition (N=15)**

Parameter	Dienogest	Estradiol	Estrone
C_{max}	85.2 (19.7) ng/ml	70.5 (25.9) pg/ml	483 (198) pg/ml
T_{max} (hr)[a]	1.5 (1–2)	3 (1.5–12)	4 (3–12)
AUC(0–24hr)	828 (187) ng·hr/ml	1323 (480) pg·hr/ml	7562 (3403) pg·hr/ml
$t_{½}$ (hr)	12.3 (1.4)	NA	NA

[a] Median (range) for T_{max}

C_{max} = Maximum serum concentration

T_{max} = Time to reach maximum concentration

AUC(0–24hr) = Area under the concentration-time curve from 0 hr data point up to 48 hr post-administration

NA: Data not available

Food Effect

Concomitant food intake in women resulted in a 28% decrease for dienogest C_{max} and 23% increase of estradiol C_{max} while the exposure (AUC) of both dienogest and estradiol did not change.

Distribution

In serum, 38% of estradiol is bound to sex hormone-binding globulin (SHBG), 60% to albumin and 2–3% circulates in free form. An apparent volume of distribution of approximately 1.2 L/kg was determined after intravenous (IV) administration.

A relatively high fraction (10%) of circulating dienogest is present in the free form, with approximately 90% being bound non-specifically to albumin. Dienogest does not bind to SHBG and corticosteroid-binding globulin (CBG). The volume of distribution at steady state ($V_{d,ss}$) of dienogest is 46 L after the IV administration of 85 mcg ^{3}H-dienogest.

Metabolism

After oral administration of estradiol valerate, approximately 3% of the dose is directly bioavailable as estradiol. Estradiol undergoes an extensive first-pass effect and a considerable part of the dose administered is already metabolized in the gastrointestinal mucosa. The CYP 3A family is known to play the most important role in human estradiol metabolism. Together with the pre-systemic metabolism in the liver, about 95% of the orally administered dose becomes metabolized before entering the systemic circulation. The main metabolites are estrone and its sulfate or glucuronide conjugates.

Dienogest is extensively metabolized by the known pathways of steroid metabolism (hydroxylation, conjugation), with the formation of endocrinologically mostly inactive metabolites. CYP3A4 was identified as a predominant enzyme catalyzing the metabolism of dienogest.

Excretion

Estradiol and its metabolites are mainly excreted in urine, with about 10% being excreted in the feces. The terminal half-life of estradiol is approximately 14 hours.

Dienogest is mainly excreted renally in the form of metabolites and unchanged dienogest is the dominating fraction in plasma. The terminal half-life of dienogest is approximately 11 hours.

Use in Specific Populations

Pediatric Use: Safety and efficacy of Natazia has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

Geriatric Use: Natazia has not been studied in postmenopausal women and is not indicated in this population

Renal Impairment: The pharmacokinetics of Natazia has not been studied in subjects with renal impairment.

Hepatic Impairment: The pharmacokinetics of Natazia has not been studied in subjects with hepatic impairment. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. *[See Contraindications (4) and Warnings and Precautions (5.3).]*

Body Mass Index: The efficacy of Natazia in women with a BMI of > 30 kg/m^2 has not been evaluated.

Drug Interactions

Consult the labeling of all concurrently used drugs to obtain further information about interactions with oral contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Combined Oral Contraceptives

***CYP3A4 Inducers*:** Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include barbiturates, bosentan, felbamate, griseofulvin, oxcarbazepine, and topiramate. Counsel women to use an alternative method of contraception or a back-up method when moderate or weak enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Dienogest is a substrate of CYP3A4. Women who take medications that are strong CYP3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) should not choose Natazia as their oral contraceptive while using these inducers and for at least 28 days after discontinuation of these inducers due to the possibility of decreased contraceptive efficacy.

The effect of the CYP3A4 inducer rifampicin was studied in an open-label, non-randomized, single center study in 16 healthy postmenopausal women. All volunteers received a treatment regimen of 2 mg estradiol valerate and 3 mg dienogest combination tablets, dosed once daily over 17 days, and of rifampicin, which was administered once daily in an oral dose of 600 mg on Days 12 to 16. 24–hr pharmacokinetics of estradiol and dienogest on Days 11 and 17 were compared. Co-administration of rifampicin with estradiol valerate/dienogest tablets led to a 52 % and 83% decrease in the mean C_{max} and AUC(0–24hr), respectively, for dienogest and a 25% and 44% decrease in C_{max} and AUC(0–24hr), respectively, for estradiol at steady state.

Strong CYP3A4 Inhibitors: Strong CYP3A4 inhibitors such as ketoconazole increase hormone serum concentrations. The effect of a strong CYP3A4 inhibitor, ketoconazole, on dienogest and estradiol pharmacokinetics was studied in an open-label, two parallel-groups, one-sequence, one-way crossover study in healthy postmenopausal Caucasian women. One tablet of 2 mg estradiol valerate and 3 mg dienogest was administered orally once a day for 14 days. Twelve volunteers received an oral dose of 400 mg ketoconazole (that is, 2 tablets containing 200 mg ketoconazole) once daily for 7 days (Days 8–14). Twenty-four hour pharmacokinetics of estradiol and dienogest on Days 7 and 14 were compared. Co-administration with the strong inhibitor ketoconazole resulted in a 186% and 57% increase of AUC (0–24hr) at steady state for dienogest and estradiol. There was also a 94% and 65% increase of C_{max} at steady state for dienogest and estradiol when co-administered with ketoconazole.

Moderate CYP3A4 Inhibitors: Moderate CYP3A4 inhibitors such as erythromycin increase hormone serum concentrations. The effect of a moderate CYP3A4 inhibitor, erythromycin on dienogest and estradiol pharmacokinetics was studied in an open-label, two parallel-groups, one-sequence, one-way crossover study in healthy postmenopausal Caucasian women. One tablet of 2 mg estradiol valerate and 3 mg dienogest was administered orally once a day for 14 days. Twelve volunteers received an oral dose of 500 mg erythromycin three times a day for 7 days (Days 8–14). Twenty-four hour pharmacokinetics of estradiol and dienogest on Days 7 and 14 were compared. When co-administered with the moderate inhibitor erythromycin, the AUC (0–24hr) of dienogest and estradiol at steady state were increased by 62% and 33%, respectively. There was also a 33% and 51% increase of C_{max} at steady state for dienogest and estradiol when co-administered with erythromycin.

Other known CYP3A4 inhibitors such as azole antifungals, cimetidine, verapamil, macrolides, diltiazem, antidepressants, and grapefruit juice may increase plasma concentrations of dienogest and estradiol.

HIV/HCV Protease Inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of the estrogen and progestin have been noted in some cases of co-administration of HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro studies with human CYP enzymes did not indicate an inhibitory potential of dienogest at clinically relevant concentrations.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month carcinogenicity study in mice dosed orally with dienogest by gavage with doses of 5, 15 and 50 mg/kg/day (males) and 10, 30 and 100 mg/kg/day (females), the systemic exposures in the females were 1.1, 3.5, and 10.6 times the exposure (AUC of dienogest) of women taking a 3 mg dose. A statistically significantly higher incidence of stromal polyps of the uterus was observed in females given 100 mg/kg. In a similar study in rats given 1, 3, and 10 mg/kg for 104 weeks, 0.2, 1.4, and 6.1 times the exposure of women taking a 3 mg dose, there were no statistically significant drug-related neoplasms.

Dienogest was not mutagenic in *in vitro* reverse mutation tests in bacteria, in chromosome aberration tests in human peripheral lymphocytes, mouse lymphoma cells, and Chinese hamster lung cells, and tests of unscheduled DNA synthesis (UDS) in rat and human liver cells. Dienogest was also negative in an *in vivo* mouse micronucleus test, a rat liver initiation-promotion model, and an *in vitro/in vivo* UDS test in female rats.

13.2 Animal Toxicology and/or Pharmacology

Nonclinical studies in animals and *in vitro*, have shown that besides progestogenic activities, DNG is devoid of estrogenic, androgenic, glucocorticoid and mineralocorticoid activities.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trials

The study conducted in North America (U.S. and Canada) was a multicenter, open-label, single-arm, unintended pregnancy study. There were 490 healthy subjects between 18 and 35 years of age (mean age: 25.1 years) who were treated for up to 28 cycles of 28 days each. The racial demographic of enrolled women was: Caucasian (76%), Hispanic (13%), African-American (7%), Asian (3%), and Other (1%). The weight range for treated women was 40 to 100 kg (mean weight: 62.5 kg) and the BMI range was 14 to 30 kg/m^2 (mean BMI: 23.3 kg/m^2). Of treated women, 15% discontinued the study treatment due to an adverse event, 13% were lost to follow up, 10% withdrew their consent, 8% discontinued due to other reason, 1% discontinued due to protocol deviation, and 1% discontinued due to pregnancy.

The study conducted in Europe (Germany, Austria and Spain) was a multicenter, open-label, single-arm contraceptive reliability study. There were 1,377 healthy subjects between 18 and 50 years of age (mean age: 30.3 years) who were treated for 20 cycles of 28 days each. The racial demographic of enrolled women was predominantly Caucasian (99.2%). The weight range for treated women was 38 to 98 kg (mean weight: 63.8 kg) and the BMI range was 15 to 31.8 kg/m^2 (mean BMI: 22.8 kg/m^2). Of treated women, 10% discontinued the study treatment due to an adverse event, 5% discontinued due to other reason, 2% were lost to follow up, 2% discontinued due to protocol deviation, 2% withdrew their consent, and 1% discontinued due to pregnancy.

The Pearl Index (PI) was the primary efficacy endpoint used to assess contraceptive reliability and was assessed in each of the two studies, assuming all subjects were at risk of pregnancy in all medication cycles unless back-up contraception was documented. The PI is based on pregnancies that occurred after the onset of treatment and within 7 days after the last pill

intake. Cycles in which conception did not occur, but which included the use of back-up contraception, were not included in the calculation of the PI. The PI also includes patients who did not take the drug correctly. The estimated PI for the North American study is 1.64 and the estimated PI for the European study is 1.04. The Kaplan-Meier method was also used to calculate the contraceptive failure rate.

The summary of the Pearl Indexes and cumulative contraceptive failure rates are provided in Table 2:

Table 2: Summary of the Pearl Indexes and the Cumulative Contraceptive Failure Rates

Study	Age Group	Relative Treatment Exposure Cycles[1]	Number of Pregnancies within 13 Cycles and 7 Days after Last Treatment	Pearl Index	Upper Limit of 95% CI	Contraceptive Failure Rate at the End of First Year
North America	18–35	3,969	5	1.64	3.82	0.016
Europe	18–35	11,275	9	1.04	1.97	0.010

[1] Total treatment exposure time without back-up contraception

14.2 Heavy Menstrual Bleeding Clinical Trials

The efficacy and safety of Natazia were evaluated in two multi-regional, multicenter, double-blind, randomized, placebo-controlled clinical trials. Study 308960 was performed in the United States and Canada and Study 308961 was performed in Australia and 9 European countries. The studies were identical in design. The studies enrolled women, 18 years of age or older, with a diagnosis of dysfunctional uterine bleeding characterized as heavy, prolonged and/or frequent bleeding without organic pathology. Heavy menstrual bleeding (HMB) was defined as menstrual blood loss of 80 mL or more in at least 2 bleeding episodes. The diagnosis of HMB was documented through the collection of used sanitary protection (pads and tampons) to quantify blood loss assessed by the alkaline hematin method. Overall, about 85% of the subjects qualified for the study because they had heavy menstrual bleeding symptoms.

A total of 421 women with a mean age of 38.2 and a mean BMI of 25.5 were randomized to the two clinical studies, for a total of 269 women in the Natazia group and 152 women in the placebo group, and treated for seven 28-day cycles. Approximately 81% were Caucasian, 13% were Black, and 6% were Hispanic or Asian or Other.

The primary efficacy variable was the proportion of subjects who were completely relieved of symptoms, which was defined by the number of subjects with the absence of any dysfunctional bleeding symptom and who met up to 8 strictly defined criteria for success during the 90-day efficacy assessment phase. In Study 308960, the proportion of the intent-to-treat subjects with complete symptom relief was 29.2% in the Natazia group compared to 2.9% in the placebo group. In Study 308961, the proportion of the intent-to-treat subjects with complete symptom relief was 29.5% in the Natazia group compared to 1.2% in the placebo group. In both studies, Natazia was effective in treating the symptoms of HMB in women who entered the study with symptoms specific to HMB. Among patients with HMB, menstrual blood loss (MBL) was statistically significantly reduced in the group treated with Natazia compared with placebo ($p<0.0001$ for both studies). Figures 1 and 2 display the MBL volume by cycle and by study.

Figure 1: Median Menstrual Blood Loss Volume by Cycle (Study 308960)

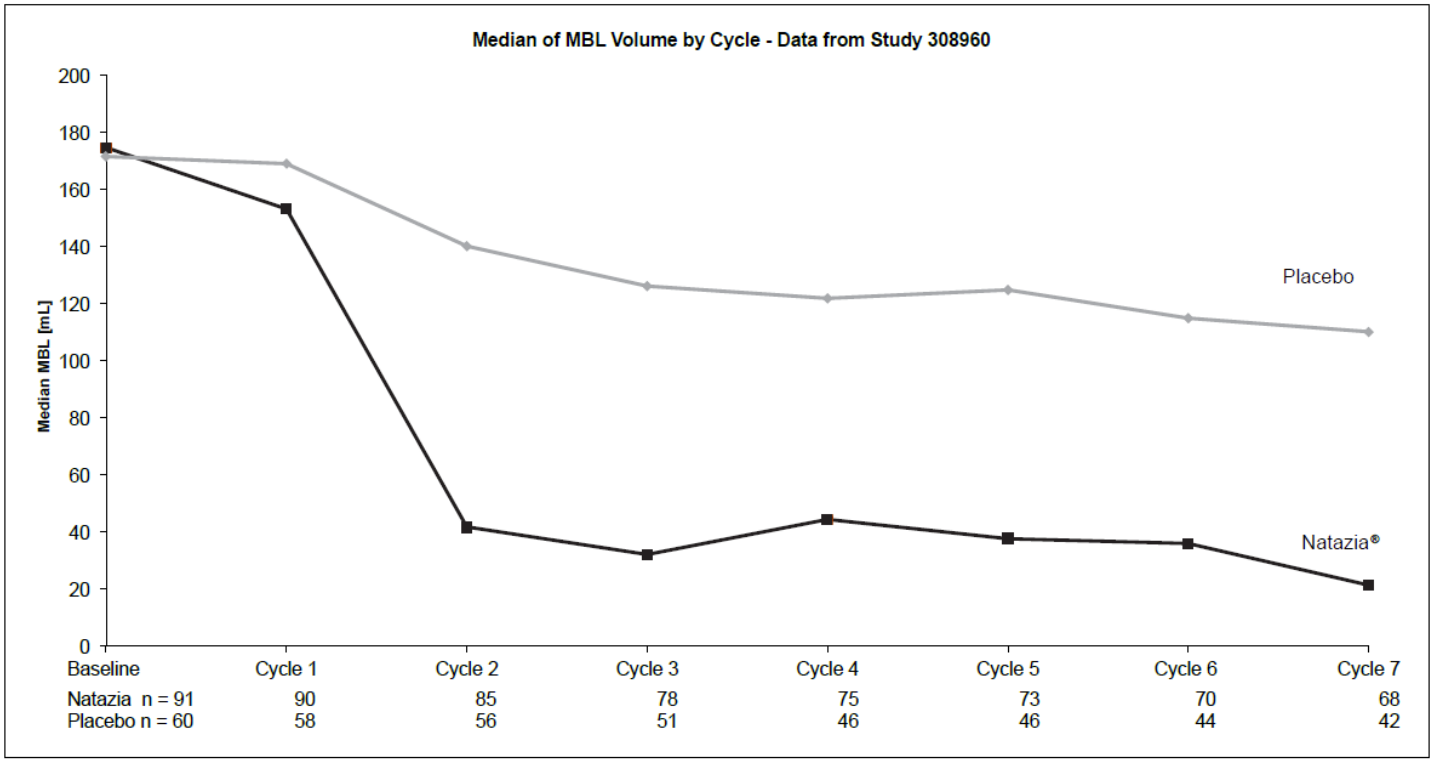
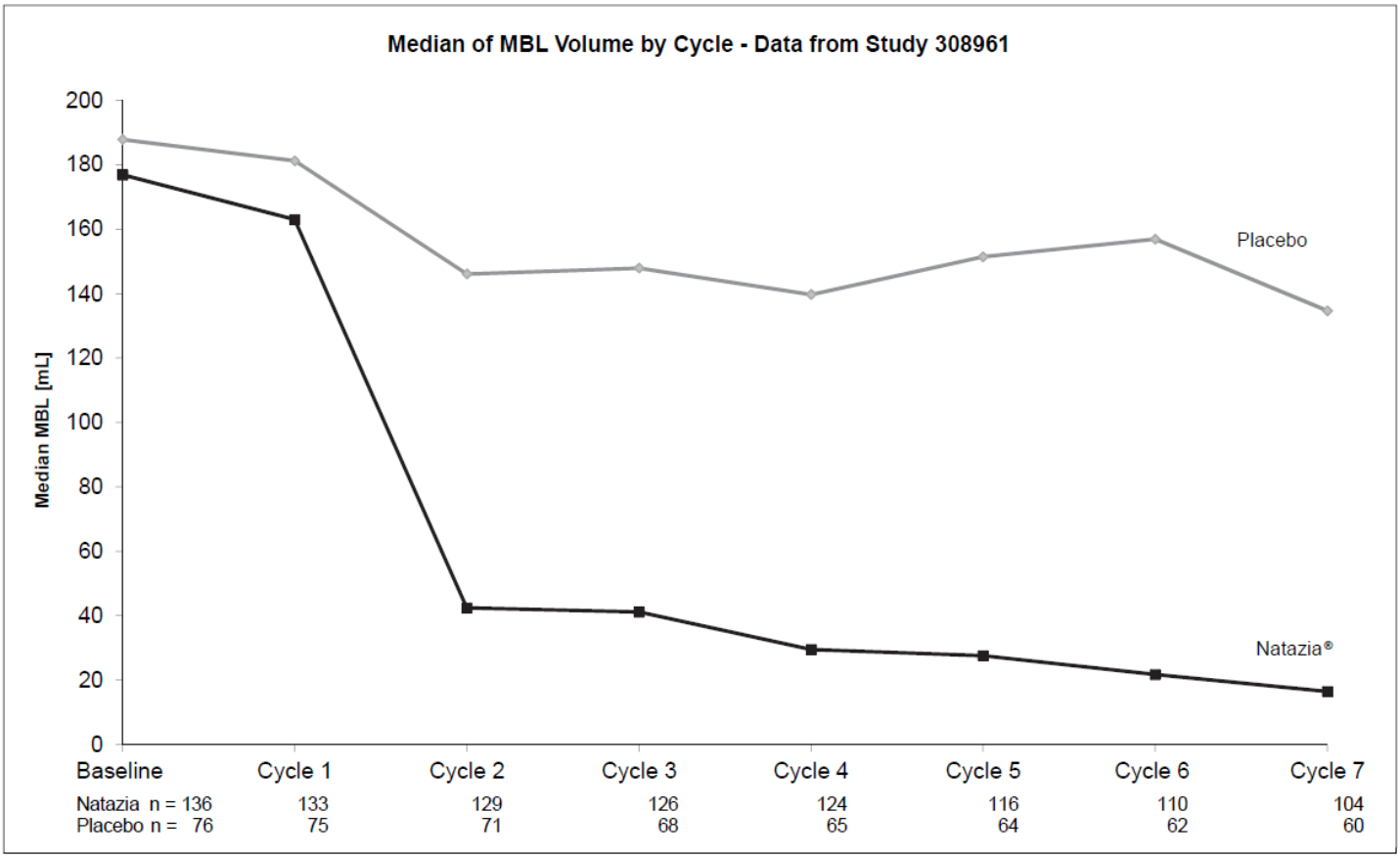


Figure 2: Median Menstrual Blood Loss Volume by Cycle (Study 308961)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Natazia (estradiol valerate and estradiol valerate/dienogest) tablets are available in packages of three blister packs (NDC 50419-409-03).

The active and inert film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with the letters DD or DJ or DH or DN or DT.

Each blister pack (28 film-coated tablets) contains in the following order:

- 2 round biconvex dark yellow film-coated tablets with embossed “DD” in a regular hexagon on one side each containing 3 mg estradiol valerate
- 5 round biconvex medium red film-coated tablets with embossed “DJ” in a regular hexagon on one side each containing 2 mg estradiol valerate and 2 mg dienogest
- 17 round biconvex light yellow film-coated tablets with embossed “DH” in a regular hexagon on one side each containing 2 mg estradiol valerate and 3 mg dienogest
- 2 round biconvex dark red film-coated tablets with embossed “DN” in a regular hexagon on one side each containing 1 mg estradiol valerate
- 2 white round biconvex white film-coated tablets with embossed “DT” in a regular hexagon on one side (inert)

16.2 Storage

Store at 25º C (77º F); excursions permitted to 15–30°C (59–86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

See "FDA-approved patient labeling (Patient Information)."

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.
- Counsel patients that Natazia does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Inform patients that Natazia is not indicated during pregnancy. If pregnancy occurs during treatment with Natazia, instruct the patient to stop further intake.
- Counsel patients to take one tablet daily by mouth at the same time every day in the exact order noted on the blister. Instruct patients what to do in the event pills are missed. *See* ***What Should I Do if I Miss any Pills*** *section in* ***FDA-Approved Patient Labeling****.*
- Counsel women who are taking strong CYP3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) not to choose Natazia as their oral contraceptive due to the possibility of decreased contraceptive efficacy.
- Counsel patients to use a back-up or alternative method of contraception when weak or moderate enzyme inducers are used with Natazia.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken Natazia for 9 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

FDA-Approved Patient Labeling

Guide for Using Natazia

WARNING TO WOMEN WHO SMOKE

Do not use Natazia if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Natazia?

Natazia is a birth control pill. It contains two female hormones, an estrogen called estradiol valerate and a progestin called dienogest. Estradiol valerate is a synthetic estrogen that is converted to estradiol in your body.

Natazia is used to treat heavy menstruation (your monthly period) that is not caused by any diagnosed conditions of the uterus (womb) in women who decide to use an oral contraceptive for birth control. Talk to your healthcare provider to determine if your bleeding is heavier than normal.

How Does Natazia Work?

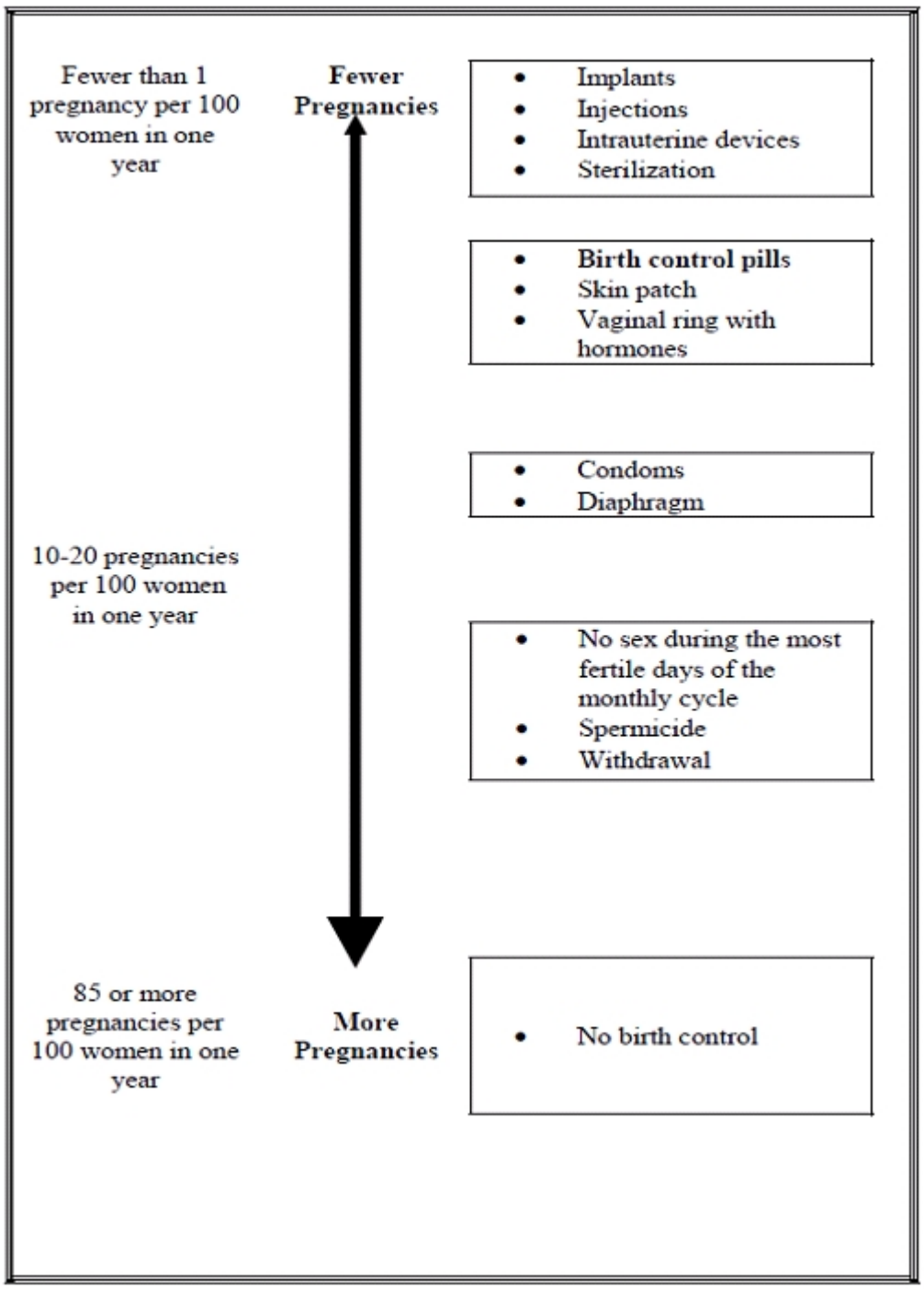
Birth control pills prevent your ovaries from producing and releasing mature eggs. Natazia decreases menstrual bleeding by thinning the lining of the uterus.

How Well Does Natazia Work For Contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of two clinical studies, 1 to 2 women out of 100 women may get pregnant during the first year they use Natazia.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Well Does Natazia Work For Heavy Menstrual Bleeding?

In two clinical trials in women with heavy menstrual bleeding who were treated with Natazia, their menstrual bleeding was reduced by an average of 78% in one trial and 72% in the other. For women treated with placebo, their menstrual bleeding was reduced by an average of 14% and 32% in the two trials, respectively.

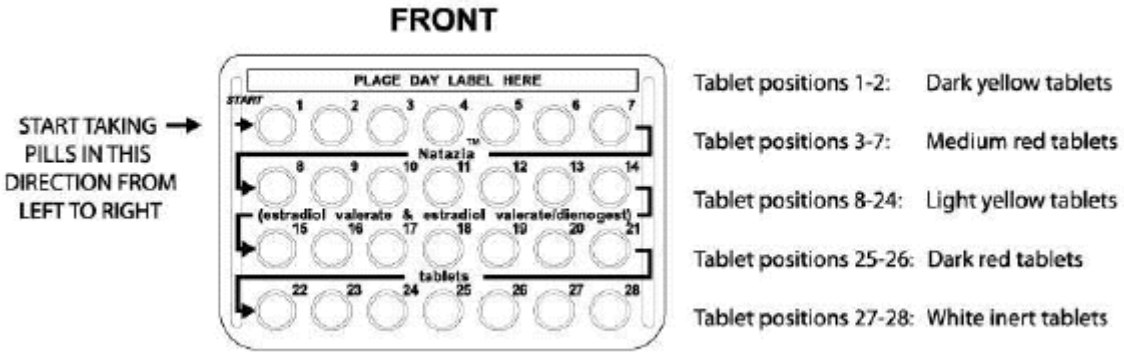
How Do I Take Natazia?

- Take one pill every day at the same time. Take the pills in the order directed on the blister pack.

- Do not skip pills or delay taking your pill by more than 12 hours. If you miss pills (including starting the pack late), you could get pregnant. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Natazia, talk to your healthcare provider about how to make pill-taking easier, or about using another method of birth control.
- You may have spotting or light bleeding when you first take Natazia. Spotting or light bleeding is normal at first.
- You may feel sick to your stomach (nauseous), especially during the first few months that you take Natazia. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea doesn't go away, call your healthcare provider.
- If you vomit or have diarrhea within 4 hours of taking your pill, follow the instructions for “What Should I Do if I Miss any Pills.”
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

Before you start taking Natazia

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on the blister pack.



- Look at your Natazia blister pack. The blister pack has 4 rows of 7 pills each, for a total of 28 pills. Find:
  - where on the pack to start taking your pills
  - in what order to take the pills

Each NATAZIA blister pack has 28 pills

- 2 dark yellow pills with hormones, for Days 1 and 2
- 5 medium red pills with hormones for Days 3–7
- 17 light yellow pills with hormones for Days 8–24
- 2 dark red pills with hormones for Days 25 and 26

- 2 white pills without hormones for Days 27 and 28

- After taking the last white pill (day 28) of the blister pack, start taking the first dark yellow pill from a new blister pack the very next day whether or not you are having your period.
- Be sure to have ready at all times another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills.
- It is not uncommon to miss a period. However, if you miss 2 periods in a row or feel like you may be pregnant, call your healthcare provider. If you are pregnant, you should stop taking Natazia.

When to Start Natazia

If you start taking Natazia and you did not use a hormonal birth control method before:

- Take the first dark yellow pill on the first day (Day 1) of your natural menstrual cycle. The first day of your menstrual cycle is the first day you start spotting or bleeding.
- Use non-hormonal back-up contraception such as a condom and spermicide for the first 9 days that you take Natazia.

If you start taking Natazia and you are switching from a combination hormonal method such as:

- another pill
- vaginal ring
- patch

- Take the first dark yellow pill on the first day of your period. Do not continue taking the pills from your previous birth control pack. If you do not have a period, contact your healthcare provider before you start Natazia.
- If you previously used a vaginal ring or transdermal patch, you should start using Natazia on the day the ring or patch is removed.
- Use a non-hormonal back-up method such as a condom and spermicide for the first 9 days you take Natazia.

If you start taking Natazia and you are switching from a progestin-only method such as a:

- progestin-only pill
- implant
- intrauterine system
- injection

- Take the first dark yellow pill on the day you would have taken your next progestin-only pill or on the day of removal of your implant or intrauterine system or on the day when you would have had your next injection.
- Use a non-hormonal back-up method such as a condom and spermicide for the first 9 days you take Natazia.

What Should I Do if I Miss any Pills

If you forgot to start a new blister pack, **you may already be pregnant.** Use back-up contraception (such as condoms and spermicides) anytime you have sex. Call your healthcare provider if you are unsure whether you are pregnant.

- Do not take more than 2 pills in one day. On the days you take 2 pills to make up for missed pills, you may feel a little sick to your stomach (nauseous).
- If you start vomiting or have diarrhea within 4 hours of taking your pill, take another pill of the same color from your extra blister pack.

If you are less than 12 hours late taking your pill

- Take your pill as soon as you remember.
- Take the next pill at the usual time.
- You do not need to use back-up contraception.

If you miss ONE PILL for more than 12 hours

Days 1–17

- Take your missed pill immediately.
- Take your next pill at the usual time (you may have to take two pills that day).
- Use back-up contraception for the next 9 days
- Continue taking one pill each day at the same time for the rest of your cycle.

Days 18–24

- Do not take any pills from your current blister pack and throw the pack away.
- Take Day 1 pill from a new blister pack.
- Use back-up contraception for the next 9 days.
- Continue taking one pill from the new blister pack at the same time each day.

Days 25–28

- Take your missed pill immediately.
- Take your next pill at the usual time (you may have to take two pills that day).
- No back-up contraception is needed.
- Continue taking one pill each day at the same time for the rest of your cycle.

If you miss TWO PILLS in a row

Days 1–17 (if you miss the pills for Days 17 and 18, follow the instructions for Days 17–25 instead)

- Do not take the missed pills. Instead, take the pill for the day on which you first noticed you had missed pills.
- Use back-up contraception for the next 9 days.

- Continue taking one pill each day at the same time for the rest of your cycle.

<u>Days 17–25</u> (if you miss the pills for Days 25 and 26, follow the instructions for Days 25–28 instead)

- Do not take any pills from your current blister pack and throw the pack away.
- Take Day 3 pill from a new blister pack.
- Use back-up contraception for the next 9 days.
- Continue taking one pill from the new blister pack at the same time each day.

<u>Days 25–28</u>

- Do not take any pills from your current blister pack and throw the pack away.
- Start a new pack on the same day or start a new pack on the day you usually start a new pack.
- No back-up contraception is needed.
- Continue taking one pill from the new pack at the same time each day, for the rest of your cycle.

You may already be pregnant or COULD BECOME PREGNANT if you had sex on the days after the pills were missed. The more pills missed and the closer they are to the end of the cycle, the higher the risk of a pregnancy. You should call your healthcare provider if you are unsure whether you are already pregnant.

If you are still not sure of what to do about the pills you have missed:

- Call your healthcare provider
- Use back-up contraception (such as condoms and spermicides) anytime you have sex and keep taking 1 pill each day

Who Should Not Take Natazia?

Your healthcare provider will not give you Natazia if you have:

- Ever had breast cancer or any cancer that is sensitive to female hormones
- Liver disease, including liver tumors
- Ever had blood clots in your arms, legs, or lungs
- Ever had a stroke
- Ever had a heart attack
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine can't control
- Diabetes with kidney, eye, or blood vessel damage
- Certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision

If any of these conditions happen for the first time while using Natazia, stop taking Natazia right away and talk to your healthcare provider. You should use non-hormonal contraceptive measures when you stop using Natazia.

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are pregnant
- Have any unexplained bleeding from the vagina

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

What Else Should I Know about Taking Natazia?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills according to directions
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Natazia, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

Tell your healthcare provider about all medicines and herbal products that you take. You should not choose Natazia as your birth control pill if you take carbamazepine, phenytoin, rifampicin or St. John's wort, because these medicines may make Natazia ineffective. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your healthcare provider you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more.

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness

- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat levels in the blood
- Depression, especially if you have had depression in the past.

Call your healthcare provider immediately if you have any thoughts of harming yourself.

- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Natazia?

Irregular vaginal bleeding or spotting may occur while you are taking Natazia. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Also, your menstrual period while using oral contraceptives may be shorter and lighter than usual. Some women may not have a menstrual period but this should not be cause for alarm as long has you have taken the pills according to direction.

What if I Miss My Scheduled Period when Taking Natazia?

It is not uncommon to miss your period. However, if you miss more than two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your

healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Natazia if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

General Advice about Natazia

Your healthcare provider prescribed Natazia for you. Please do not share Natazia with anyone else. Keep Natazia out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

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