PharmaNote®

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NATAZIA®: A NEW COMBINATION ORAL CONTRACEPTIVE

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In the U.S., the leading method of contraception is the combination oral contraceptive pill. More than 10 million women aged 15-44 years use the birth control pill as their primary method of contraception.[1]

Since the first BCP approval in 1960, the FDA has approved many oral contraceptive products. Most of these products use ethinyl estradiol (EE) along with one of many progestins approved for use. Natazia®, from Bayer HealthCare Pharmaceuticals, is a new oral contraceptive approved in May 2010 for the prevention of pregnancy that utilizes a novel estrogen, estradiol valerate (E2V), and progestin, dienogest (DNG).[2] While there are many multi-phasic oral contraceptives on the market, Natazia® (E2V/DNG) is the first four-phase product available. E2V/DNG utilizes an estrogen step-down dosing and progestin step-up dosing approach to control the menstrual cycle and prevent ovulation.[3] This article will review the unique components of E2V/DNG, its pharmacology, adverse effects, and results of recent clinical trials.

PHARMACOLOGY & PHARMACOKINETICS

Mechanism of Action

Combination oral contraceptives contain both an estrogen and progestin. The estrogen component inhibits ovulation by suppressing follicle stimulating hormone (FSH), while the progestin changes the cervical mucus to prevent sperm from fertilizing the ovum.[4]

E2V is a synthetic prodrug of 17β-estradiol. E2V is metabolized quickly into estradiol and then metabolized into other active metabolites via CYP3A4. A potential advantage of E2V over EE is the reduced occurrence of negative effects on serum lipids and lipoproteins that is seen with doses of EE as low as 10 mcg.[5,6] A 2 mg average daily dose of E2V provides the same biological effects on the hypothalamic-pituitary-ovarian axis as 20 mcg of EE and has neutral effects on serum lipids.[3,6]

DNG is a fourth-generation progestin with high specificity for the progesterone receptor.[3,7] DNG shows anti-androgenic but no estrogenic, glucocorticoid, gonadotropic, or anti-mineralocorticoid activity in humans.[3,7] The anti-androgenic properties reduce side effects such as hirsutism, acne, and weight gain. Negative effects on blood pressure may be lessened due to DNG's lack of glucocorticoid activity. The absence of anti-mineralocorticoid activity reduces the chance of hyperkalemia seen with other new progestins; however, DNG does not cause diuresis.

Pharmacokinetics

Table 1 outlines some of the pharmacokinetic parameters of E2V and DNG. Food increases the absorption for E2V and decreases the absorption for DNG, but does not affect drug exposure to the patient (AUC).

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Table 1 | Serum pharmacokinetic parameters of dienogest, estradiol, and estrone at steady-state.[4]

Parameter	Dienogest	Estradiol	Estrone
Cmax	85.2 ng/mL	70.5 pg/mL	483 pg/mL
Tmax (hr)	1.5	3	4
AUC(0-24hr)	828 ng·hr/mL	1323 pg·hr/ml	7562 pg·hr/ml
$t_{1/2}$ (hr)	12.3	NA	NA

Values taken 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).

E2V/DNG is excreted in both the urine and feces.

Clinical Trials

Three trials led to the FDA approval of E2V/DNG. Study 1 was a multicenter, open-label, non-comparative 20-cycle study conducted in Europe between April 2004 and July 2006. The primary outcome was the number of observed pregnancies which was estimated using the Pearl Index. Of the women treated in the study, 10% discontinued therapy due to an adverse event and 1% discontinued due to pregnancy (**Table 2**).[3]

Study 2 was conducted in North America and was a multicenter, open-label, single-arm, unintended pregnancy study. Of treated women, 15% discontinued the therapy due to an adverse event and 1% discontinued due to pregnancy (**Table 2**).[4]

Study 3 was a multicenter, double-blind, double-dummy, randomized study conducted in 34 centers in Germany, the Czech Republic and France, between March 2005 and September 2006. This study compared the bleeding pattern, cycle control and safety of E2V/DNG with that of a monophasic regimen of 20 mcg EE/0.1 mg levonorgestrel (LNG). The primary outcomes were bleeding pattern and cycle control parameters. Cycle control parameters included the incidence and characteristics of scheduled (withdrawal) and unscheduled (intracyclic) bleeding (**Table 3**).[8]

Adverse Drug Reactions

E2V/DNG has a similar adverse drug reactions profile to other oral contraceptives (**Table 4**). The major ADRs include serious cardiovascular events, vascular effects, and liver disease. Some common but less serious ADRs include irregular uterine bleeding, nausea, breast tenderness, and headache. Breakthrough bleeding occurrs in 10-23% of women who use E2V/DNG.[4] In one study, no significant difference was observed in breakthrough bleeding rates—14% (E2V/DNG) vs. 12% (EE/LNG) (**Table 3**).[8] However, the comparator used in the study has a higher incidence of breakthrough bleeding when compared to other currently available BCPs.[9] Comparisons of breakthrough bleeding with BCPs containing the newer progestins are currently lacking.

Contraindications

The contraindications for E2V/DNG are no different than other oral contraceptives and include patients at high risk of venous or arterial thrombotic diseases, those with undiagnosed abnormal genital bleeding, breast cancer or other estrogen or progestin sensitive cancer, liver disease, and pregnancy.

E2V/DNG labeling contains a boxed warning against smoking because of the increased risk of cardiovascular side effects. Women who smoke should be strongly advised not to use combination oral contraceptives.[4]

Special Populations

Nursing Mothers

Nursing mothers should avoid estrogen products because estrogen can reduce milk production. Barrier methods of contraception can be used safely in this

Table 2 | Summary of the pearl index and cumulative contraceptive failure rates from phase III data.[4]

Study	Age Group (yrs)	Relative Treatment Exposure Cycle[a]	Number of Pregnancies within 13 Cycles and 7 Days after Last Treatment	Pearl Index	Uppper Limit of 95% CI[b]	Contraceptive Failure Rate at the End of First Year
Study 1[3]	18-35	11,275	9	1.04	1.97	0.010
Study 2[4]	18-35	3,969	5	1.64	3.82	0.016

[a] Total treatment exposure time without back-up contraception.
[b] Pearl Index value is based on actual use.

Table 3 | Study 3 (phase III trial) outcomes.[8]

Outcome Measure	E2V/DNG	EE/LNG	P value
Bleeding Pattern			
Period 1	17.3	21.5	p<0.001
Period 2	13.4	15.9	p<0.001
Withdrawal Bleeding/Cycle[a]	77.7-83.2%	89.5-93.8%	p<0.001
Intracyclic Bleeding	14% (10.5% to 18.6%)	12% (9.9% to 17.1%)	NS

NS = not significantly different.
[a] Measured over 7 cycles.

population. Additionally, small amounts of oral contraceptive hormones (and their metabolites) have been found in breast milk.[4]

Renal Impairment

Safety and efficacy has not been evaluated in those with renal impairment, but dosage adjustment should not be necessary, since E2V/DNG is metabolized hepatically.[4]

Hepatic Impairment

The safety and efficacy of E2V/DNG has not been studied in patients with hepatic impairment, although the manufacturer recommends against its use in this population.[4]

Body Mass Index

The safety and efficacy of E2V/DNG has not been established in patients with a BMI >30 kg/m^2.[4]

Drug Interactions

E2V/DNG is metabolized primarily through CYP 3A4. Inducers of this metabolic pathway may decrease the efficacy of the product (**Table 5**). Antibiotics may also decrease the efficacy of E2V/DNG by decreasing the gut flora that is involved in the enterohepatic recirculation of the hormones.

Table 4 | Adverse events reported in phase III trials.

	Number of Women (%)	
Adverse Event	**Study 1**	**Study 3**
Breast pain	50 (3.6)	13 (3.3)
Acne	36 (2.6)	5 (1.3)
Headache	26 (1.9)	7 (1.8)
Metrorrhagia	26 (1.9)	NR
Weight increase	21 (1.5)	2 (0.5)
Breast Discomfort	17 (1.2)	NR
Alopecia	NR	3 (0.8)
Migraine	NR	2 (0.5)

NR = not reported.

Dosing & Administration

Like other multiphasic oral contraceptives, the tablets contained within each pack of E2V/DNG vary in strength and are color-coded based on the dose of E2V or DNG (**Table 6**). Patients should start E2V/DNG on the first day of their menstrual cycle and continue to take one tablet daily.

While the once daily administration for E2V/DNG is no different than other oral contraceptives, the criteria for what is considered a "missed dose" is more strict with E2V/DNG than with most oral contraceptives. Usually, a dose is considered "missed" if it is taken more than 24 hours after the intended time; however, the package insert for E2V/DNG considers a "missed dose" to be one that is delayed by more than 12 hours. If a patient misses a dose by more than 12 hours during days 1-17, she is instructed to use a backup method of contraception for the next nine days. If a dose is missed by more than 12 hours on days 18-24, a new pack should be started. If a dose is missed on day 25-28, no back-up method of contraception is required.

Table 5 | CYP 3A4 Inducers.

• aminoglutethimide	• efavirenz
• amprenavir	• ethosuximide
• aprepitant	• etravirine
• bosentan	• garlic supplements
• carbamazepine	• glucocorticoids
• dexamethasone	• glutethimide
• griseofulvin	• phenytoin
• modafinil	• primidone
• nafcillin	• rifabutin
• nevirapine	• rifampin
• oxcarbazepine	• rifapentine
• phenobarbital	• ritonavir
• St. John's wort	

Table 6 | Dosing and tablet descriptions of E2V/DNG.

Color of Tablet	Dose	Day of Cycle to Administer
Dark yellow	3mg E2V	1-2
Medium red	2mg E2V; 2mg DNG	3-7
Light yellow	2mg E2V; 3mg DNG	8-24
Dark red	1mg E2V	25-26
White	Inert	27-28

Cost

The average retail cost of Natazia® is approximately $89.50 per month with a range of $76.68-$98.59.

Summary

Natazia® is a newly approved oral contraceptive utilizing a novel estrogen (estradiol valerate) and progestin (dienogest). Due to its unique pharmacology, E2V/DNG may cause less side effects and may decrease the negative impact on lipids that is often seen with other oral contraceptives. Current data shows potential for this product to be an option for women with hypertension or elevated cholesterol, however, insufficient evidence exists currently to justify choosing Natazia® over less expensive products. Though current data confirms the efficacy of the product as another option for contraception, further investigation should be conducted to verify the metabolic benefits of this combination over currently available BCPs.

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JALYN® (DUTASTERIDE/TAMSULOSIN): A NEW OPTION IN BPH

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Benign prostatic hyperplasia (BPH) affects approximately 14 million men in the United States. The annual cost of treatment of BPH in the United States is $4 billion dollars.[1] Current therapies available for BPH include alpha-adrenergic blockers, 5-alpha-reductase inhibitors, or surgical treatment.[2] Jalyn® (dutasteride/tamsulosin) is the first FDA-approved combination product to treat symptomatic BPH in men with an enlarged prostate.[3,4] Dutasteride/tamsulosin is manufactured by GlaxoSmith-Kline and was approved by the FDA in June 2010.[4] The objectives of this article are to discuss the pharmacology, clinical trials, dosage and administration, drug interactions, safety and tolerability, special precautions, and cost of dutatsteride/tamsulosin.

Pharmacology

Mechanism of Action

Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT) by competitively inhibiting type I and type II 5-alpha-reductase. DHT binds to androgen receptors in the prostate and promote cell proliferation.[5] The reduction of DHT by dutasteride is dose-dependent and observed within 1 to 2 weeks. The median serum DHT concentrations after one to two weeks of treatment can be reduced by 85-90%. Tamsulosin works by blocking alpha-1-adrenoreceptors which causes smooth muscle in the bladder neck and prostate to relax improving urine flow rate and reducing symptoms of BPH.[3]

Pharmacokinetics & Pharmacodynamics

Dutasteride significantly increases total testosterone (97.1 ng/dL, P<0.003) and thyroid stimulating hormone (0.4 mcIU/mL, P<0.05) compared to placebo, both of which returned to baseline 24 weeks after stopping dutasteride.[3] Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%). Dutasteride is metabolized by CYP3A4 and CYP3A5.[3]

Tamsulosin is also highly bound to plasma proteins (94%-99%). **Table 1** contains the pharmacokinetic data of dutasteride and tamsulosin under single-dose and fed conditions.

Clinical Trials

The Combination of Avodart and Tamsulosin trial (CombAT) is the only trial to date that has studied the efficacy of dual therapy using tamsulosin and dutasteride coadministered as separate capsules. The CombAT study was a 4-year, multicenter, randomized, double-blind parallel group study that enrolled 4844 men over the age of fifty. Sixty-six percent of the men completed the trial.[7,8] The clinical progression of BPH was measured using the International Prostate Symptom Score (IPSS) which assigns a numerical value to the severity of BPH symptoms.[7-9] Combination therapy reduced the relative risk of the primary endpoint, time to first acute urinary retention (AUR) or BPH-related surgery, by 66% compared to tamsulosin monotherapy (p<0.001) (**Table 2**). When combination therapy was compared to dutasteride monotherapy, no significant difference was found regarding time to first AUR or BPH related surgery. In regards to the relative risk of BPH clinical progression, combination therapy was found to significantly reduce the risk compared to monotherapy of either agent. Maximum urinary flow rate was significantly improved by combination therapy compared to tamsulosin monotherapy, but not dutasteride monotherapy.

The Medical Therapy of Prostatic Symptoms (MTOPS) study also examined combination therapy to treat BPH. Patients were randomly assigned to treatment with the alpha-adrenergic receptor antagonist doxazosin, the 5-alpha reductase inhibitor finasteride, a combination of the two, or placebo. The endpoints for this study were overall clinical progression, changes in time of the AUA symptom score, maximal urinary flow rate, invasive treatments related to BPH, and changes in PSA level and prostate volume over time. The MTOPS study lasted for 4.5 years and enrolled 3047 men. Combination therapy reduced the clinical progression of BPH significantly more than did either monotherapy or placebo. Additionally, combination therapy and finasteride monotherapy reduced the long-term risk of AUR and the need for invasive therapy.[10]

The Prospective European Doxazosin and Combination Therapy (PREDICT) trial enrolled 1095 men and compared treatment of doxazosin, finasteride, and combination therapy for 52 weeks. The PREDICT trial looked at similar endpoints as the other BPH trials (**Table 3**). The authors concluded that alpha-blocker therapy, in this case with doxazosin, is effective as a monotherapy for BPH and no additional benefit is provided by adding finasteride.[11]

The Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group was a 52 week study, randomly assigning 1229 participants to finasteride, terazosin, or a combination of the two. The VA Co-op study also used some of the same endpoints as CombAT and MTOPS. However, the study authors concluded that the combination of terazosin and finasteride was not superior to terazosin alone.[12] One reason for the discrepancy may be due to the difference in selectivity and potency between dutasteride and finasteride. Dutasteride is selective for type I and II 5-alpha

Table 1 | Pharmacokinetic parameters of dutasteride and tamsulosin.[3]

Component	N	AUC (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$
dutasteride	92	39.6 (23.1)	2.14 (0.77)	3.00 (1.00-10.00)	5 weeks*[6]
tamsulosin	92	187.2 (95.7)	11.3 (4.44)	6.00 (2.00-24.00)	13.5hr (3.92)

*Data obtained from package insert for dutasteride, not obtained under single-dose and fed conditions.[6]

Table 2 | Results of the CombAT trial.[8]

	Dutasteride	Tamsulosin	Dutasteride/Tamsulosin
First acute urinary retention (AUR) or first BPH-related surgery at given time point			
At 12 months	27 events; 1623 at risk (1.7%)	40 events; 1611 at risk (2.5%)	29 events; 1610 at risk (1.8%)[a]
At 24 months	49 events; 1484 at risk (3.3%)	102 events; 1464 at risk (7.0%)	43 events; 1457 at risk (3.0%)[a]
At 36 months	65 events; 1365 at risk (4.8%)	146 events; 1307 at risk (11.1%)	58 events; 1347 at risk (4.3%)[a]
At 48 months	84 events; 1277 at risk (6.6%)	191 events; 1176 at risk (16.2%)	67 events; 1274 at risk (5.3%)[a]
Proportion with ≥ 3 point IPSS ↑ (clinical BPH progression at month 48)			
	66%	59%	71%[b]
Maximum urinary flow rate at month 48			
	2.0 mL/s increase (p = 0.05)	0.7 mL/s increase	2.4 mL/s increase[a]
Prostate volume at month 48			
	28% decrease	4.6% increase	27.3% decrease[a]

Values are not statically significantly different unless otherwise noted.
[a] p<0.001 for combination therapy compared to tamsulosin.
[b] p<0.001 for combination therapy compared to tamsulosin and dutasteride monotherapy.

-reductase and is about 60 times more potent than finasteride.[13] Because finasteride is only specific for type I 5-alapha reductase, it only suppresses approximately 70% of serum DHT and 85-90% of DHT in the prostate. Dutasteride has been found to almost completely suppress DHT.[14]

Dosing & Administration

Dutasteride/tamsulosin is available in a fixed dose combination of 0.5 mg dutasteride and 0.4 mg of tamsulosin. Dutasteride/tamsulosin should be administered once daily and should be swallowed whole. The capsule should not be chewed, crushed, or opened. Dutasteride/tamsulosin may be administered without regard to food; however, a 30% mean decrease in tamsulosin C_{max} has been observed when given with food. Dutasteride/tamsulosin does not require any dose-adjustment in the elderly, renally impaired, or hepatically impaired. Tamsulosin exposure may be greater in geriatric males due to decreased intrinsic clearance; however no dose-adjustment is required.[3]

Drug Interactions

Drug interaction studies have not been done using dutasteride/tamsulosin; the information available at this time is from these agents use as monotherapy (**Table 4**).[3]

Safety & Tolerability

No trials have been completed with dutasteride/tamsulosin in a single capsule to determine the side effects.[3] The current information that is available is from trials that used monotherapy as well as coadministered separate capsules. The most common adverse effects associated with these agents are sexual in nature (**Table 5**).

Table 3 | Baseline parameters & endpoint values in the PREDICT trial.[11]

Parameter	Doxazosin	Finasteride	Combination	Placebo
Mean baseline total IPSS	17.1 ± 4.2	17.1 ± 4.4	17.3 ± 4.7	17.2 ± 4.5
Mean endpoint IPSS	8.7 ± 5.8	10.9 ± 6.2	8.7 ± 6.2	11.8 ± 6.9
LS mean change from baseline at endpoint IPSS	-8.3 ± 0.4	-6.6 ± 0.4	-8.5 ± 0.4	-5.7 ± 0.4
Mean baseline Qmax (mL/s)	10.4 ± 2.5[a,b]	10.2 ± 2.5[a]	10.4 ± 2.7[a]	10.8 ± 2.5
Mean endpoint Qmax	14.0 ± 4.9	12.1 ± 4.7	14.5 ± 5.1	12.1 ± 4.2
LS mean change from baseline at endpoint Qmax	3.6 ± 0.3	1.8 ± 0.3	3.8 ± 0.3	1.4 ± 0.3

IPSS = International Prostate Symptom Score; **LS** = least squares; **Qmax** = maximal urinary flow rate.
Values represented as the mean ± standard deviation or LE mean ± standard error.
[a] P ≤ 0.0001 vs. placebo
[b] P = 0.09 vs. finasteride

Table 4 | Drug interactions with dutasteride/tamsulosin.

Medication	Interaction/Effect
Strong CYP3A4 inhibitors • ketoconazole	Significantly decreases tamsulosin metabolism increasing exposure
Moderate CYP3A4 inhibitors • erythromycin	Potential for increase in tamsulosin exposure
Strong or moderate CYP2D6 inhibitors • paroxetine • terbinafine	Potential for increase in tamsulosin exposure
Phosphodiesterase inhibitors • sildenafil • tadalafil • vardenafil	Coadministration can cause vasodilation resulting in symptomatic hypotension
Cimetidine	Cimetidine decreases the clearance of tamsulosin resulting in an increase in AUC

Special Precautions

Patients using dutasteride/tamsulosin should be instructed to avoid donating blood while taking this medication. Donation of blood may occur six months after the last dose of dutasteride/tamsulosin is administered. This precaution is in place to prevent exposure of dutasteride to pregnant women to whom this medication is contraindicated.[3]

Due to the risk of Intraoperative Floppy Iris Syndrom (IFIS) associated with tamsulosin use, patients should be instructed to notify their ophthalmologist if they are taking dutasteride/tamsulosin.[3]

Patients should also be counseled on the possibility of priapism and the importance of seeking medical attention immediately if this occurs.[3]

Patients should be counseled that any women of child bearing age should not handle dutasteride/tamsulosin. Dutasteride may be absorbed through the skin and result in exposure to the fetus.[3]

Cost Effectiveness

The average retail price for a one month supply of dutasteride, which is only available as a branded product, is $123.31, whereas the average retail price for a one month supple of tamsulosin, which is available generically, is $103.02. The average cost of purchasing the two agents separately is $226.33.

The average retail price for a one month supply of Jalyn® (dutasteride/tamsulosin) is $130.32.

Table 5 | Adverse events from the CombAT trial.[7]

	Combination, % (n=1610)	Dutasteride, % (n=1623)	Tamsulosin, % (n=1611)
Any adverse event	73	73	72
Any serious adverse event	19	21	22
Any drug-related adverse event	28[a]	21	19
Any serious drug-related adverse event	<1	<1	<1
Any adverse event leading to study withdrawal	13	12	14
Any drug-related adverse event leading to study withdrawal	6	4	4
Erectile dysfunction	9	7	5
Retrograde ejaculation	4	<1	1
Altered (decreased) libido	4	3	2
Ejaculation failure	3	<1	<1
Semen volume decreased	2	<1	<1
Loss of libido	2	1	1
Dizziness	2	<1	2
Gynacomastia	2	2	<1
Nipple pain	1	<1	<1
Breast tenderness	1	1	<1

[a] p<0.01 for each of the comparisons of combination to dutasteride and tamsulosin.

SUMMARY

BPH is a condition that affects millions of men in the United States and results in a significant amount of healthcare spending each year. Dutasteride/tamsulosin represents a new option for the treatment of BPH as the first combination medication for BPH. Dutasteride/tamsulosin provides the convenience of a single capsule with once daily dosing and cost savings compared to purchasing both products separately. The CombAT and MTOPS trial have provided new evidence supporting combination therapy to treat BPH. However, the VA Study and PREDICT trial concluded that combination therapy was no more efficacious than monotherapy with an alpha-blocker alone.[10,11] Dutasteride and tamsulosin are newer, more selective agents which may account for the discrepancy with older studies that used less selective medications in combination for the treatment of BPH. When choosing therapy for BPH, one must examine the available data and select the appropriate therapy based on what is the best for the patient.

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