FINASTERIDE

STERCIA

1 mg Film-Coated Tablet

5α-Reductase inhibitor

℞

FORMULATION

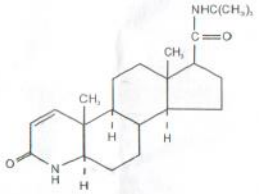
Each film-coated tablet contains :

Finasteride, USP 1 mg

DESCRIPTION

Finasteride, a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide, N-(1, 1-dimethylethyl)-3-oxo-,(5α,17β). The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water.

Finasteride tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: Lactose monohydrate, microcrystalline cellulose, starch, sodium starch glycolate, docusate sodium, magnesium stearate, opadry II pink, purified water.

Finasteride 1 mg is available as tan colored, octagonal covex film coated tablets.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approxinately one-third of circulating DHT. The Type II 5-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), in vitro binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme (IC_{50} = 500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibitions by finasteride are accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1 mg tablet. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

PHARMACOKINETICS

Absorption

In a study of 15 healthy young male subjects, the mean bioavailability of finasteride 1 mg tablets was 65% (range, 26 to 170%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. At steady state following dosing with 1 mg/day (n=12), maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9 to 13.7 ng/mL) and was reached 1 to 2 hours postdose; $AUC_{(0\ to\ 24\ hr)}$ was 53 ng•hr/mL (range, 20 to 154 ng•hr/mL). Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 liters (range, 44 to 96 liters; n=15). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing.

Finasteride has been found to cross the blood-brain barrier.

Metabolism

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites, have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

Excretion

Following intravenous infusion in healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70 to 279 mL/min). Mean terminal half-life in plasma was 4.5 hours (range, 3.3 to 13.4 hours; n=12). Following an oral dose of ^{14}C-finasteride in man (n=6), a mean of 39% (range, 32 to 46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51 to 64%) was excreted in the feces.

Mean terminal half-life is approximately 5 to 6 hours in men 18 to 60 years of age and 8 hours in men more than 70 years of age.

SPECIAL POPULATIONS

Pediatric : Finasteride pharmacokinetics have not been investigated in patients <18 years of age.

Gender : Finasteride tablets are not indicated for use in women.

Geriatric : No dosage adjustment is necessary in the elderly. Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance. (See also PHARMACOKINETICS, Excretion and PRECAUTIONS, Geriatric Use sections).

Race : The effect of race on finasteride pharmacokinetics has not been studied.

Renal Insufficiency : No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks, where exposure of these patients to metabolites would presumably be much greater.

Hepatic Insufficiency : The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of finasteride tablets in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Mean (SD) Pharmacokinetic Parameters in Healthy Men	
	Mean (±SD) n=15
Bioavailability	65% (26 - 170 %)*
Clearance (mL/min)	165 (55)
Volume of distribution (L)	76 (14)

Mean (SD) Non compartmental Pharmacokinetic Parameters After Multiple Doses of 1 mg/day in Healthy Men (ages 19 to 42)	
	Mean (±SD) n=12
AUC (ng•hr/mL)	53 (33.8)
Peak Concentration (mg/mL)	9.2 (2.6)
Time to Peak (hours)	1.3 (0.5)
Half-Life (hours)*	4.5 (1.6)

*First-dose values; all other parameters are last-dose values

INDICATIONS

Finasteride tablets are indicated for the treatment of men with male pattern hair loss (androgenetic alopecis) to increased hair growth and prevent further hair loss.

Finasteride tablets are not indicated for use in women (see PRECAUTIONS, Pregnancy) or children.

Finasteride tablets are not effective in postmenopausal women with androgenetic alopecia.

CONTRAINDICATIONS

Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of Type II 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See PRECAUTIONS, Information for Patients). In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Finasteride is contraindicated for hypersensitivity to any component of this medication.

WARNINGS

Finasteride tablets are not indicated for use in pediatric patients (see INDICATIONS, PRECAUTIONS, Pediatric Use) or women (see also PRECAUTIONS, Information for Patients).

PRECAUTIONS

General

Caution should be used in the administration of finasteride tablets in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

Information for Patients

Women should not handle crushed or broken finasteride tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to the male fetus. Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS and PRECAUTIONS, Pregnancy)

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

Physicians should instruct their patients to read the patient package insert before starting therapy with finasteride tablets and to read it again each time the prescription is renewed so that they are aware of current information for patients regarding finasteride tablets.

Drug/Laboratory Test Interactions

Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxin, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary- testicular axis was not affected.

In clinical studies with finasteride tablets 1 mg in men 18 to 41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at month 12. Further, in clinical studies with finasteride tablets 5 mg when used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. These findings should be taken into account for proper interpretation of serum PSA when evaluating men treated with finasteride.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug-metabolizing enzyme system. Compounds that have been tested in man have include antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Other Concomitant Therapy

Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with Zacetaminophen, acetylsalicylic acid, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory (NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0 \text{ to } 24 \text{ hr})}$ for animals and mean $AUC_{(0 \text{ to } 24 \text{ hr})}$ for man (0.05 mcg.hr/mL).

No evidence of mutagenicity was observed in an in vitro bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an in vitro alkaline elution assay. In an in vitro chromosome aberration assay, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. In an in vivo chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1824 times the human exposure) as determined in the carcinogenicity studies.

Pregnancy

Teratogenic Effects : Pregnancy Category X (See CONTRAINDICATIONS).

Finasteride tablets are not indicated for use in women.

Nursing Mothers

Finasteride tablets are not indicated for use in women. It is not known whether finasteride is excreted in human milk.

Pediatric Use

Finasteride tablets are not indicated for use in pediatric patients. Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical efficacy studies with finasteride tablets did not include subjects aged 65 and over. Based on the pharmacokinetics of finasteride 5 mg, no dosage adjustment is necessary in the elderly for finasteride tablets (see CLINICAL PHARMACOLOGY, Pharmacokinetics). However the efficacy of finasteride tablets in the elderly has not been established.

ADVERSE REACTIONS

Clinical Studies for finasteride tablets 1 mg in the Treatment of Male Pattern Hair Loss

In three controlled clinical trials for finasteride tablets of 12-month duration, 1.4% of patients taking finasteride tablets (n=945) were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo; n=934).

Clinical adverse experiences that were reported as possibly, probably or definitely drug-related in >1% of patients treated with finasteride tablets or placebo are presented in below table.

Drug-Related Adverse Experiences for Finasteride tablets 1 mg in Year 1 (%) MALE PATTERN HAIR LOSSS

	Finasteride tablets N=945	Placebo N=934
Decreased Libido	1.8	1.3
Erectile Dysfunction	1.3	0.7
Ejaculation Disorder (Decreased Volume of Ejaculate	1.2 (0.8)	0.7 (0.4)
Discontinuation due to drug- related sexual adverse experiences	1.2	0.9

OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride tablets can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1,500 mg/m² (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m² (400 mg/kg) and 5,900 mg/m² (1,000mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg orally once a day. Finasteride tablets may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit, which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months.

AVAILABILITY

Alu/Alu Blister pack of 7 tablets (Box of 28 tablets).

STORAGE AND HANDLING

Store at temperatures not exceeding 30°C.
Protect from moisture.

NOTE: Read the instructions thoroughly before use.
Please do not use the drug after expiry date.
Keep out of reach of children.

CAUTION: Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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For suspected adverse drug reaction, report to the FDA:
www.fda.gov.ph

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