PRODUCT CIRCULAR

PROPECIA®
(finasteride)

I. THERAPEUTIC CLASS

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

II. INDICATIONS

PROPECIA is indicated for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

PROPECIA is **not** indicated for use in women (see PREGNANCY and *Studies in women*) or children.

III. DOSAGE AND ADMINISTRATION

The recommended dosage is one 1-mg tablet daily. PROPECIA may be taken with or without food.

In general, daily use for 3 months or more is necessary before increased hair growth and/or prevention of further hair loss is observed. Continued use is recommended to obtain maximum benefit. Withdrawal of treatment leads to reversibility of effect within 12 months.

IV. CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Finasteride is a competitive and specific inhibitor of Type II 5α -reductase. Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT), resulting in significant decreases in serum and tissue DHT concentrations. Circulating levels of testosterone were increased by approximately 10-15% compared with placebo, yet remained within the physiologic range. Finasteride produces a rapid reduction in serum DHT concentration, reaching significant suppression within 24 hours of dosing.

Hair follicles contain Type II 5α -reductase. In men with male pattern hair loss, the balding scalp contains miniaturized hair follicles and increased amounts of DHT. Administration of finasteride decreases scalp and serum DHT concentrations in these men. Men with a genetic deficiency of Type II 5α -reductase do not suffer from male pattern hair loss. These data and the results of the clinical studies confirm that finasteride inhibits the process responsible for miniaturization of the scalp hair follicles, leading to reversal of the balding process.

Studies in men

The efficacy of PROPECIA was demonstrated in three studies in 1879 men 18 to 41 years of age with mild to moderate, but not complete, vertex and frontal/mid-area hair loss. In these studies, hair growth was assessed using four separate measures including hair count, rating of photographs of the head by an expert panel of dermatologists, investigator assessment, and patient self-assessment.

In the two studies in men with vertex hair loss, treatment with PROPECIA was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning as early as 3 months. Treatment with PROPECIA for 5 years resulted in stabilization of hair loss in 90% of men based on photographic assessment and in 93% based on investigator assessment. In addition, increased hair growth was reported in 65% of men treated with PROPECIA based on hair counts (vs 0% of the placebo group), in 48% based on photographic assessment (vs 6% of the placebo group), and in 77% based on investigator assessment (vs 15% of the placebo group). In contrast, in the placebo group, gradual hair loss over time was observed in 100% of men based on hair counts (vs 35% of men treated with PROPECIA), in 75% based on photographic assessment (vs 10% of men treated with PROPECIA), and in 38% based on investigator assessment (vs 7% of men treated with PROPECIA). In addition, patient self-assessment demonstrated significant increases in hair density, decreases in hair loss, and improvement in appearance of hair over 5 years of treatment with PROPECIA. While hair improvement measures compared to baseline were greatest in men treated with PROPECIA at 2 years and gradually declined thereafter (e.g., increase of 88 hairs in a representative 5.1 cm^2 area at 2 years and increase of 38 hairs at 5 years), hair loss in the placebo group progressively worsened compared to baseline (decrease of 50 hairs at 2 years and 239 hairs at 5 years). Thus, based on all four measures, the difference between treatment groups continued to increase throughout the 5 years of the studies.

The 12-month study in men with frontal/mid-area hair loss also demonstrated significant improvements in scalp hair growth and appearance as evaluated by the same measures as those described above.

A 48-week, placebo-controlled study designed to assess the effect of PROPECIA on the phases of the hair-growth cycle (growing phase [anagen] and resting phase [telogen]) in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total, telogen, and anagen hair counts were obtained in a 1-cm^2 target area of the scalp. Treatment with PROPECIA led to improvements in anagen hair counts, while men in the placebo group lost anagen hair. At 48 weeks, men treated with PROPECIA showed net increases in total and anagen hair counts of 17 hairs and 27 hairs, respectively, compared to placebo. This increase in anagen hair count, compared to total hair count, led to a net improvement in the anagen-to-telogen ratio of 47% at 48 weeks for men treated with PROPECIA, compared to placebo. These data provide direct evidence that treatment with PROPECIA promotes the conversion of hair follicles into the actively growing phase.

In summary, these studies demonstrated that treatment with PROPECIA increases hair growth and prevents further hair loss in men with androgenetic alopecia.

Studies in women

Lack of efficacy was demonstrated in postmenopausal women with androgenetic alopecia who were treated with PROPECIA in a 12-month, placebo-controlled study (n=137). These women showed no improvement in hair count, patient self-assessment, investigator assessment, or ratings based on standardized photographs, compared with the placebo group (see INDICATIONS).

Pharmacokinetic properties

Absorption

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 80%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately 2 hours after dosing and the absorption is complete after 6-8 hours.

Distribution

Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 liters.

At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL and was reached 1-2 hours postdose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng• hr/mL.

Finasteride has been recovered in the cerebrospinal fluid (CSF) but the drug does not appear to concentrate preferentially to the CSF. A very small amount of finasteride has also been detected in the seminal fluid of subjects receiving finasteride.

Biotransformation

Finasteride is metabolized primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of ^{14}C-finasteride in man, two metabolites of finasteride were identified that possess only a small fraction of the 5α -reductase inhibitory activity of finasteride.

Elimination

Following an oral dose of ^{14}C-finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% of total dose was excreted in the feces.

Plasma clearance is approximately 165 mL/min.

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men older than 70 years of age. These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

Characteristics in Patients

No adjustment in dosage is necessary in nondialyzed patients with renal impairment.

V. CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

- Use in women when they are or may potentially be pregnant (see PREGNANCY)
- Hypersensitivity to any component of this product

PROPECIA is not indicated for use in women or children.

VI. PRECAUTIONS

In clinical studies with PROPECIA in men 18-41 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. When PROPECIA is used for treatment of male pattern hair loss in older men who also have benign prostatic hyperplasia (BPH), consideration should be given to the fact that, in older men with BPH, PSA levels are decreased by approximately 50%.

Breast cancer has been reported in men taking finasteride 1 mg during postmarketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia, or nipple discharge.

VII. PREGNANCY

PROPECIA is contraindicated for use in women when they are or may potentially be pregnant.

Because of the ability of Type II 5α -reductase inhibitors to inhibit conversion of testosterone to DHT in some tissues, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman.

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

VIII. NURSING MOTHERS

PROPECIA is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

IX. PEDIATRIC USE

PROPECIA is not indicated for use in children.

X. USE IN THE ELDERLY

Clinical studies with PROPECIA have not been conducted in elderly men with male pattern hair loss.

XI. 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 included antipyrine, digoxin, glyburide, propranolol, theophylline, and warfarin and no interactions were found.

Although specific interaction studies were not performed, in clinical studies finasteride doses of 1 mg or more were used concomitantly with ACE inhibitors, acetaminophen, alpha blockers, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

XII. SIDE EFFECTS

PROPECIA is generally well tolerated. Side effects, which usually have been mild, generally have not required discontinuation of therapy.

Finasteride for male pattern hair loss has been evaluated for safety in clinical studies involving more than 3,200 men. In three 12-month, placebo-controlled, double-blind, multicenter studies of comparable design, the overall safety profiles of PROPECIA and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 1.7% of 945 men treated with PROPECIA and 2.1% of 934 men treated with placebo.

In these studies, the following drug-related adverse experiences were reported in ≥ 1% of men treated with PROPECIA: decreased libido (PROPECIA, 1.8% vs. placebo, 1.3%) and erectile dysfunction (1.3%, 0.7%). In addition, decreased volume of ejaculate was reported in 0.8% of men treated with PROPECIA and 0.4% of men treated with placebo. Resolution of these side effects occurred in men who discontinued therapy with PROPECIA and in many who continued therapy. In a separate study, the effect of PROPECIA on ejaculate volume was measured and was not different from that seen with placebo.

The incidence of each of the above side effects decreased to ≤ 0.3% by the fifth year of treatment with PROPECIA.

OTHER LONG-TERM DATA

Finasteride has also been studied for prostate cancer risk reduction at 5 times the dosage recommended for male pattern hair loss. In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, of whom 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving finasteride 5 mg and 1147 (24.4%) men receiving placebo. In the finasteride 5 mg group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Additional analyses suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride 5 mg group may be explained by a detection bias due to the effect of finasteride 5 mg on prostate volume. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2) at diagnosis. The clinical significance of the Gleason 7-10 data is unknown.

POST-MARKETING EXPERIENCE

The following additional adverse experiences have been reported in postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity reactions such as rash, pruritus, urticaria, and angioedema (including swelling of the lips, tongue, throat, and face)
Psychiatric disorders: depression; decreased libido that continued after discontinuation of treatment, suicidal ideation
Reproductive system and breast disorders: sexual dysfunction (erectile dysfunction and ejaculation disorder) that continued after discontinuation of treatment; breast tenderness, breast enlargement and male breast cancer (see VI PRECAUTIONS); testicular pain; hematospermia; male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

XIII. 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 side effects.

No specific treatment for overdosage with PROPECIA is recommended.

XIV. AVAILABILITY

PROPECIA tablets, each containing finasteride 1 mg, are supplied in packs of 28’s and 84’s.

Product Registrant:

Organon Singapore Pte. Ltd.
150 Beach Road
#36-01/08 Gateway West
Singapore 189720

Zuellig Pharma (B) Sdn Bhd
Unit 5, 1st floor,
Spg 607, Jalan Gadong,
Kg Beribi, BSB, BE1118
Brunei Darussalam

Packed by:

Hangzhou MSD Pharmaceutical Co Ltd
199 Wen Hai North Road,
HEDA Hangzhou, Zhejiang Province China

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