PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] pms-FINASTERIDE

Finasteride Tablets

Tablets, 1 mg, Oral

House Standard

Type II 5α-reductase Inhibitor

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MAY 12, 2010

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Psychiatric	09/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-FINASTERIDE (finasteride tablets) is a Type II 5α-reductase inhibitor, indicated for:

- the treatment of male pattern hair loss (androgenetic alopecia) in men who have mild to moderate scalp hair loss of the vertex and anterior mid-scalp.

Clinical studies were conducted in men between 18 to 41 years of age.

1.1 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS; and 14 CLINICAL TRIALS).

1.2 Geriatrics (> 65 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use (see 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

pms-FINASTERIDE is contraindicated in the following:

- Pregnancy - Use in women when they are or may potentially be pregnant (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Exposure to Finasteride – Risk to Male Fetus);
- Hypersensitivity to any component of this product.

pms-FINASTERIDE is not indicated for use in women or children.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

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

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

Dosage in Renal Insufficiency: Adjustments in dosage are not necessary in patients with varying degrees of renal insufficiency (creatinine clearances as low as 0.15 mL/s [9 mL/min]) as pharmacokinetic studies did not indicate any change in the disposition of finasteride.

4.4 Administration

pms-FINASTERIDE is for oral administration.

4.5 Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

5 OVERDOSAGE

Patients have received single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months without adverse reactions.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet / 1 mg	Docusate Sodium, Hydroxypropyl Cellulose, Hypromellose, Iron Oxide Red, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Talc, Titanium Dioxide and Yellow Iron Oxide.

pms-FINASTERIDE 1 mg tablet is a tan-colored, round, biconvex, coated tablet, debossed, with "FS" on one side and "1" on the other side.

Available in a blister package of 30 tablets and HDPE bottles containing 100 tablets.

7 WARNINGS AND PRECAUTIONS

General
Caution should be used in the administration of pms-FINASTERIDE in patients with liver function abnormalities, as finasteride is metabolized in the liver.

Other causes of alopecia should be ruled out prior to prescribing pms-FINASTERIDE. Efficacy and duration of treatment should be assessed periodically by the treating physician.

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 8 ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis

Increased Risk of High-Grade Prostate Cancer with 5α-Reductase Inhibitors:

Men aged 55 and over with a normal digital rectal examination and prostate specific antigen (PSA) ≤ 3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of finasteride tablets, 1 mg) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8 –10 prostate cancer (finasteride 1.8% vs. placebo 1.1%) (see 8 ADVERSE REACTIONS). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride) (1% dutasteride vs. 0.5% placebo). 5α-reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5α-reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Monitoring and Laboratory Tests

Effects on PSA and Prostate Cancer Detection:

In clinical studies with finasteride tablets, 1 mg in men 18 – 41 years of age, the mean value of serum 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%. Other studies with finasteride tablets, 5 mg showed it may also cause decreases in serum PSA in the presence of prostate cancer. These findings should be taken into account for proper interpretation of serum PSA when evaluating men treated with finasteride.

Any confirmed increase from the lowest PSA value while on finasteride tablets, 1 mg may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance to therapy with finasteride tablets, 1 mg may also affect PSA test results.

Psychiatric

There have been post-marketing reports of serious psychiatric symptoms in patients being treated with finasteride that sometimes continued after treatment discontinuation. Mood alterations including depressed mood, depression, self-harm injury, suicidal ideation, as well as worsening of pre-existing depression (psychiatric disorder) have been reported in patients treated with finasteride (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions). It is recommended that all patients be screened for suicidal ideation, self-harm, and depression and/or associated risk factors before treatment initiation.

Clinical monitoring of all patients for signs and symptoms of psychiatric disorder should continue throughout treatment and after. If these occur, treatment should be discontinued and patients advised to seek medical advice, as soon as possible.

7.1 Special Populations

7.1.1 Pregnant Women

pms-FINASTERIDE is not indicated for use in women. Women should not handle crushed or broken pms-FINASTERIDE tablets when they are or may potentially be pregnant (see 2 CONTRAINDICATIONS). Because of the ability of Type II 5α-reductase inhibitors such as finasteride to inhibit conversion of testosterone to dihydrotestosterone, pms-FINASTERIDE may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman.

Exposure to Finasteride - Risk to Male Fetus:
Women should not handle crushed or broken tablets of pms-FINASTERIDE 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. pms-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.

7.1.2 Breast-feeding

It is not known whether pms-FINASTERIDE is excreted in human milk.

7.1.3 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 14 CLINICAL TRIALS).

7.1.4 Geriatrics (> 65 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use (see 14 CLINICAL TRIALS).

Use in Postmenopausal Women:
Results of a one-year placebo-controlled study, enrolling 137 healthy postmenopausal women with androgenetic alopecia (age range: 41 – 60 years), showed no benefit of treatment with finasteride 1 mg daily on scalp hair growth.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following clinically significant adverse effects may be associated with the treatment of pms-FINASTERIDE (see 7 WARNINGS AND PRECAUTIONS):

- Male breast cancer
- High-grade prostate cancer
- Mood disorders such as depression, self-harm injury, suicidal ideation, worsening of pre-existing depression
- Abnormalities of male fetus

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

In these studies, the following drug-related adverse reactions were reported in ≥ 1% of men treated with finasteride or placebo, respectively (see Table 2):

Table 2: Drug-Related Adverse Reactions Reported in Patients Treated with finasteride tablets in Phase 3 Clinical Trials

MedDRA terms	Finasteride Tablets, 1 mg (n = 945)	Placebo (n = 934)
Decreased libido	1.8%	1.3%
Erectile dysfunction	1.3%	0.7%
Ejaculation disorder	1.2%	0.7%
Primarily decreased volume of ejaculate	0.8%	0.4%

Integrated analysis of clinical adverse reactions showed that during treatment with finasteride tablets, 36 (3.8%) of 945 men had reported one or more of these adverse reactions as

compared to 20 (2.1%) of 934 men treated with placebo (p = 0.04). Resolution of these adverse reactions occurred in men who discontinued therapy with finasteride tablets and in most who continued therapy. In a separate study, the effect of finasteride tablets on ejaculate volume was measured and was not different from that seen with placebo (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics).

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

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At month 12, statistically significant differences were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems) when compared to placebo. However, no significant difference was seen in the question on overall satisfaction with sex life.

Long-Term Studies for Finasteride Tablets, 5 mg in the Treatment of Benign Prostatic Hyperplasia:
The PCPT trial was a 7-year randomized, double-blind, placebo-controlled trial that enrolled 18,882 healthy men ≥ 55 years of age with a normal digital rectal examination and a PSA ≤3.0 ng/mL. Men received either finasteride tablets, 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams. Biopsies were performed for elevated PSA, an abnormal digital rectal exam, or the end of study. The incidence of Gleason score 8 –10 prostate cancer was higher in men treated with finasteride (1.8%) than in those treated with placebo (1.1%).

In a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride), similar results for Gleason score 8 –10 prostate cancer were observed (1% dutasteride vs. 0.5% placebo). The clinical significance of these findings with respect to use of finasteride tablets, 1 mg by men is unknown.

No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride tablets, 5 mg. Finasteride tablets, 5 mg is not approved for the prevention of prostate cancer.

8.4 Abnormal Laboratory Findings

Clinical Trial Findings
No difference in standard laboratory parameters was observed between patients treated with placebo or finasteride.

8.5 Post-Market Adverse Reactions

The following additional adverse experiences have been reported in post-marketing 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.

Musculoskeletal and Connective Tissue Disorders: Rare cases of the following have been reported: rhabdomyolysis, myopathy, myalgia, myasthenia, and CK elevation. In some cases, these events were found to be reversible with discontinuation of finasteride therapy.

Psychiatric Disorders: Mood alterations and depression, decreased libido that continued after discontinuation of treatment. Mood alterations including depressed mood and, less frequently, suicidal ideation have been reported in patients treated with finasteride 1 mg. Patients should be monitored for psychiatric symptoms and if these occur, the patient should be advised to seek medical advice.

Reproductive System and Breast Disorders: Sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment, breast tenderness and enlargement, male breast cancer, testicular pain, hematospermia, male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect significantly the cytochrome P450-linked drug metabolizing enzyme system. Compounds which have been tested in man have included antipyrine, digoxin, glyburide, propranolol, theophylline, and warfarin and no interactions were found. However, patients on medication with narrow therapeutic indices, such as phenytoin, should be carefully monitored when treatment with pms-FINASTERIDE is initiated.

9.4 Drug-Drug Interactions

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.

9.7 Drug-Laboratory Test Interactions

In clinical studies with finasteride tablets 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 finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men > 41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking finasteride tablets, 1 mg.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

pms-FINASTERIDE is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into dihydrotestosterone (DHT). Two distinct isozymes of 5α-reductase 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 approximately one-third of circulating DHT. The Type II 5α-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 inhibition by finasteride is 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.

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. By this mechanism, finasteride interrupts a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

10.2 Pharmacodynamics

Finasteride had no effect compared to placebo on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, 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), estradiol or prolactin were detected. Gonadotropin-releasing hormone (GnRH) stimulated levels of LH or FSH were not altered, indicating that regulatory control of the hypothalamic-pituitary-testicular axis was not affected. Circulating levels of testosterone were increased by approximately 10 – 15%, compared to placebo, yet remained within the physiologic range.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of finasteride tablets (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

Finasteride appeared to inhibit both C_{19} and C_{21} steroid metabolism and hence appeared to have an inhibitory effect on both hepatic and peripheral Type II 5α-reductase activity. The serum DHT metabolites androstenediol glucuronide and androsterone glucuronide were also significantly reduced. This metabolic pattern is similar to that observed in individuals with a genetic deficiency of Type II 5α-reductase who have markedly decreased levels of DHT and who do not suffer from male pattern hair loss.

10.3 Pharmacokinetics

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1 mg tablets was 65% (range, 26 – 170%), based on the ratio of AUC relative to a 5 mg intravenous dose infused over 60 minutes. Following the intravenous infusion, mean plasma clearance was 165 mL/min (range, 70 – 279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44 – 96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

Absorption:
Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 65%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately 1 to 2 hours after dosing and the absorption is complete after 6 – 8 hours.

Distribution:
There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9 – 13.7 ng/mL) and was reached 1 to 2 hours post-dose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20 – 154 ng•hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3 – 13.4 hours).

Finasteride has been recovered in the cerebrospinal fluid (CSF) of patients treated with a 7 – 10-day course of finasteride, but the drug does not appear to concentrate preferentially to the CSF.

Metabolism:
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, a mean of 39% (range, 32 – 46%) of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% (range, 51 – 64%) of total dose was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

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 more than 70 years of age. These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

Special Populations and Conditions

- **Renal Insufficiency**
  No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 0.15 to 0.92 mL/s (9.0 – 55 mL/min), AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to values 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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C to 30°C and protect from light to prevent discoloration.

12 SPECIAL HANDLING INSTRUCTIONS

Crushed or broken tablets of pms-FINASTERIDE should not be handled by women when they are or may potentially be pregnant (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.1 Pregnant Women, Exposure to Finasteride - Risk to Male Fetus).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

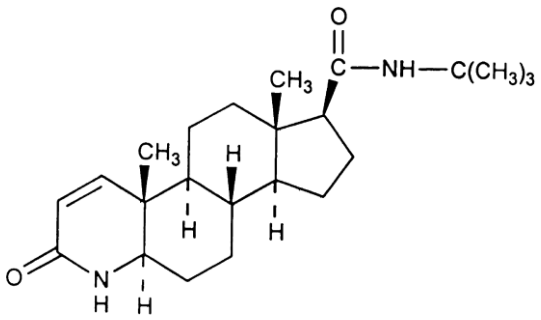
Drug Substance

Proper name: finasteride

Chemical name: N-(1, 1-dimethylethyl)-3-oxo-4-aza-5α-androst-l-ene-17β-carboxamide.

Molecular formula and molecular mass: $C_{23}H_{36}N_2O_2$; 372.55 g/mol

Structural formula:



Physicochemical Properties:

Description: finasteride is a white, crystalline solid

Solubility profile: freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water (0.05 mg/mL at 25°C).

Melting point: approximately 257°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Male Pattern Hair Loss (Androgenetic Alopecia)

Studies in Men

The efficacy of finasteride tablets was demonstrated in three studies in 1,879 men 18 – 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 finasteride tablets was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning as early as 3 months. Treatment with finasteride tablets 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 finasteride tablets 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 finasteride tablets), in 75% based on photographic assessment (vs. 10% of men treated with finasteride tablets) and in 38% based on investigator assessment (vs. 7% of men treated with finasteride tablets). 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 finasteride tablets. While hair improvement measures compared to baseline were greatest in men treated with finasteride tablets 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 finasteride tablets 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 finasteride tablets led to improvements in anagen hair counts, while men in the placebo group lost anagen hair. At 48 weeks, men treated with finasteride tablets 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 finasteride tablets, compared to placebo. These data provide direct evidence that treatment with finasteride tablets promotes the conversion of hair follicles into the actively growing phase.

In summary, these studies demonstrated that treatment with finasteride tablets 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 finasteride tablets 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 1 INDICATIONS).

14.2 Comparative Bioavailability Studies

A blinded, single-dose, randomized, two-period, two-treatment, crossover study was conducted to compare the bioavailability of finasteride from pms-FINASTERIDE 1 mg tablets (Pharmascience Inc.) and PROPECIA® 1 mg tablets (Merck Frosst Canada Ltd.) in 22 healthy male subjects 21 – 53 years of age under fasting conditions. A summary of the results is provided in the following table:

Finasteride (1 x 1 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-t} (ng·h/mL)	36.45 37.952 (27.3)	37.92 39.62 (27.9)	96.1	90.8 – 101.8
AUC_I (ng·h/mL)	38.92 40.54 (27.9)	40.22 42.12 (28.6)	96.8	91.3 – 102.6
C_{max} (ng/mL)	6.33 6.45 (19.2)	6.04 6.25 (26.7)	104.9	99.4 – 110.6
T_{max}[3] (h)	1.5 (1.00 – 3.0)	2.0 (1.0 – 3.5)		
$T_{½}$[4] (h)	4.96 (34.6)	5.13 (33.0)		

[1]pms-FINASTERIDE (finasteride) tablets, 1 mg (Pharmascience Inc.)
[2]PROPECIA® (finasteride), tablets, 1 mg (Merck Canada Ltd.,) Canada
[3]Expressed as the median (range) only
[4]Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The ability of finasteride to inhibit Type II 5α-reductase and block the formation of DHT *in vivo* was demonstrated using intact male rats and dogs. Studies were designed to demonstrate a decrease in prostatic levels of DHT or shrinkage in prostate size. Four hours after receiving a subcutaneous injection of 0.1 mg finasteride, rats showed a decrease in the concentration of DHT in the prostate. In dogs, treatment with finasteride 1 mg/kg given orally in four divided doses over an 18-hour period showed a reduction in the prostatic DHT concentration 6 hours after the final dose. These studies demonstrated that finasteride is active *in vivo* in blocking the formation of DHT.

The decreased levels of DHT also resulted in a decrease in prostate size. Prostate shrinkage was seen in intact mature dogs, which received 1 mg/kg/day of finasteride by mouth for 6 weeks. A comparison of pre- and post-treatment prostate volumes showed that finasteride induced over 40% reduction in prostate size. A similar effect was noted in immature castrated male rats treated with testosterone. Finasteride, at oral doses of 0.1 mg/day, significantly inhibited the growth effect of exogenous testosterone on the accessory sex glands. This response is due to the specific inhibition of Type II 5α-reductase, as 2.5 mg/day of finasteride failed to block the ability of exogenous DHT to stimulate growth of the seminal vesicles and ventral prostate in treated animals.

Finasteride has no direct anti-androgen activity as shown by its lack of affinity for the androgen receptor in rat prostate cytosol. Concentrations of finasteride as high as 10^{-4}M did not prevent the binding of ^{3}H-DHT whereas unlabelled DHT inhibited the binding with an IC_{50} of 2.9 nM.

Standard assays conducted in rats, mice and rabbits demonstrated that finasteride does not inhibit gonadotropin secretion or exhibit any antiestrogenic, uterotropic, antiprogestational, androgenic, or progestational activity. These data are consistent with finasteride acting as a specific Type II 5α-reductase inhibitor with no other hormonal effects.

In a hepatotoxicity test, 40 mg/kg/day of finasteride was given orally to dogs for 28 days. Venous blood was analyzed for ALT (SGPT) and AST (SGOT). Neither transaminase was increased; illustrating that finasteride did not cause liver damage.

Ancillary pharmacology studies to assess effects on organ systems and biological parameters were conducted with finasteride. No important changes were seen in renal, gastric, and respiratory function in dogs nor in the cardiovascular system of dogs and rats.

General Toxicology:

Table 3: Acute Toxicity

Species	Sex	Finasteride Route	LD_{50} mg/kg
Mouse	Male	Oral	596
	Female	Oral	486
	Male	Intraperitoneal	391
	Female	Intraperitoneal	372
Rat	Male	Oral	967
	Female	Oral	418
	Male	Intraperitoneal	1,027
	Female	Intraperitoneal	885
	Male	Subcutaneous	> 2,000
	Female	Subcutaneous	> 2,000
Dog	Male	Oral	> 1,000

Subacute and Chronic Toxicity Studies

The nature of the treatment-related changes in laboratory animals treated with finasteride tablets are shown in Table 4.

Table 4: Finasteride Target Organs Observed in Animal Studies

Treatment-Related Changes		Species	No Effect Dose (mg/kg/day)
Epididymal vacuolation (head)		Rat	0.1
Testes	- Leydig cell hyperplasia	Rat	20
		Mouse	2.5
	- Leydig cell adenoma	Mouse	25
Liver	- increased weight	Mouse	2.5
		Rat	5
		Dog	15
Thyroid	- increased weight	Rat	5
Increased serum alkaline phosphatase		Dog	5

For most of the treatment-related changes seen in laboratory animals, a clear no-effect dose has been defined. Furthermore, most of the observed treatment-related effects can be categorized under three broad headings based on the current understanding of the drug-induced changes (Table 5).

Table 5: Treatment-Related Changes Seen in Laboratory Animals

Treatment-Related Changes	Species
• **Resulting from inhibition of 5α-reductase**	
- Decreased accessory sex glands weight	Rats, mice, dogs
- Epididymis (head), vacuolation	Rats
- Developmental effects in male fetuses	Rats
- Decreased fertility in males	Rats
• **Resulting from altered endocrine balance**	
- Leydig cell hyperplasia	Rats, mice
- Leydig cell adenoma	Mice
• **Resulting from induction of drug metabolizing enzymes**	
- Increased liver weight	Mice, rats, dogs
- Increased thyroid weight	Rats

Carcinogenicity
No evidence of a tumorigenic effect was observed in a 24-month study in rats receiving doses of finasteride up to 320 mg/kg/day (16,000 times the recommended human dose of 1 mg/day).

In a 19-month carcinogenicity study in mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenoma was observed at a dose of 250 mg/kg/day (12,500 times the recommended human dose of 1 mg/day); no adenomas were seen in mice given 2.5 or 25 mg/kg/day (125 and 1,250 times the recommended human dose of 1 mg/day, respectively [Table 4]).

In mice at a dose of 25 mg/kg/day and in rats at a dose of ≥ 40 mg/kg/day (1,250 and ≥ 2,000 times the recommended human dose of 1 mg/day, respectively), an increase in the incidence of Leydig cell hyperplasia was observed.

A positive correlation between the proliferative changes of the Leydig cells and the increase in serum luteinizing hormone (LH) levels (2 – 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride (Table 4).

No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for one year, at doses of 20 mg/kg/day and 45 mg/kg/day (1,000 and 2,250 times the recommended human dose of 1 mg/day, respectively) or in mice treated for 19 months, at a dose of 2.5 mg/kg/day (125 times the recommended human dose of 1 mg/day [Table 4]).

Genotoxicity:
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, when Chinese hamster ovary cells were treated with high concentrations (450 – 550 mcmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000 – 22,000 times the peak plasma levels

in man given a total dose of 1 mg. Furthermore, the concentrations (450 – 550 mcmol) used in the *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increases in chromosome aberration were observed with finasteride at the maximum tolerated dose (250 mg/kg/day; 12,500 times the recommended human dose of 1 mg/day).

Reproductive and Developmental Toxicology
In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,000 times the recommended human dose of 1 mg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen.

In sexually mature rats treated with the same dose of finasteride, there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility and fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment.

The decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man who does not form copulatory plugs. No drug-related effect on testes or on mating performance has been seen in rats or rabbits.

Dose-dependent development of hypospadias, at an incidence of 3.6 to 100%, were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 mcg/kg/day to 100 mcg/kg/day (5 to 5,000 times the recommended human dose of 1 mg/day). Additionally, pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at doses ≥ 30 mcg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day), and decreased anogenital distance when given finasteride in doses ≥ 3 mcg/kg/day (approximately one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced has been defined in male rats as Days 16 – 17 of gestation.

The changes described above are expected pharmacological effects of Type II 5α-reductase inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed *in utero* to finasteride are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Administration of finasteride to rats during the late gestation and lactation period resulted in slightly decreased fertility in first generation male offspring (3 mg/kg/day; 150 times the recommended human dose of 1 mg/day). No developmental abnormalities have been observed in first generation male or female offspring resulting from mating finasteride-treated male rats

(80 mg/kg/day; 4,000 times the recommended human dose of 1 mg/day) with untreated females.

No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from Days 6 – 18 of gestation at doses up to 100 mg/kg/day (5,000 times the recommended human dose of 1 mg/day).

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20 – 100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PROPECIA® (tablets, 1 mg), submission control 275154, Product Monograph, Organon Canada Inc., November 24, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-FINASTERIDE
Finasteride Tablets

Read this carefully before you start taking **pms-FINASTERIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-FINASTERIDE**.

What is pms-FINASTERIDE used for?
pms-FINASTERIDE is used in adult men for the treatment of male pattern hair loss. This condition is also known as androgenetic alopecia.

How does pms-FINASTERIDE work?
pms-FINASTERIDE prevents the production of a hormone called DHT (dihydrotestosterone) in the scalp. DHT causes a decrease of hair growth and thinning of the hair. This can lead to male pattern hair loss. The lowered level of DHT in the scalp leads to increased hair growth.

What are the ingredients in pms-FINASTERIDE?
Medicinal Ingredient: Finasteride
Non-medicinal ingredients: Docusate sodium, Hydroxypropyl Cellulose, Hypromellose, Iron Oxide Red, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Talc, Titanium Dioxide and Yellow Iron Oxide.

pms-FINASTERIDE comes in the following dosage forms:
Tablet: 1 mg

Do not use pms-FINASTERIDE if:
- you are allergic to finasteride, any ingredient in pms-FINASTERIDE or component of its container.
- you are a women or child. Women who are or may potentially be pregnant must not use pms-FINASTERIDE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-FINASTERIDE. Talk about any health conditions or problems you may have, including if you:
- have liver disease

Other warnings you should know about:

Monitoring and testing

- pms-FINASTERIDE may increase your chance of a more serious form of prostate cancer. You may undergo a blood test called Prostate-Specific Antigen (PSA) test. The PSA test is for the screening of prostate cancer. PROPECIA can alter PSA values. If you have a PSA test done, you should tell the healthcare professional administering the test that you are taking PROPECIA.
- Your healthcare professional will check your PSA levels during your treatment.
- You should monitor your breasts regularly. Speak to your healthcare provider immediately if you notice any changes. This may include lumps, pain or nipple discharge, breast enlargement, and tenderness.

Pregnancy

- Women who are or may be pregnant must not use pms-FINASTERIDE.
- They should also not handle crushed or broken tablets of pms-FINASTERIDE. A male baby may be harmed if a pregnant women is exposed to the medicinal ingredient in pms-FINASTERIDE. It may cause the male baby to be born with abnormalities of the sex organs. A pregnant woman may be exposed if the tablet is absorbed through the skin.
  pms-FINASTERIDE tablets are coated to prevent contact with the medicinal ingredient during normal handling (i.e., tablets are not broken or crushed).
- Speak to a healthcare professional if a pregnant woman comes into contact with the active ingredient in pms-FINASTERIDE.

Behaviour and mood changes

- There have been reports that finasteride tablets may cause changes in mood including extreme sadness (depression), injuries from hurting yourself on purpose (self-harm injury), and thoughts of suicide (suicidal ideation). These mental health problems may continue even after you stop treatment.
- Tell your healthcare professional if you have had these behaviour and mood changes before. They should check your mental health before, during and after your treatment with pms-FINASTERIDE.
- If you feel sad, want to hurt yourself, or end your own life or if others around you notice changes in your behaviour, get medical help right away.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take pms-FINASTERIDE:

- Take pms-FINASTERIDE exactly as your healthcare professional has prescribed.
- Take by mouth with or without food.

Usual dose:

Take one 1 mg tablet once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-FINASTERIDE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
If you missed a dose of this medication, you do not need to make up the missed dose. Skip the missed dose and continue with your next scheduled dose. Do not take two doses at the same time.

What are possible side effects from using pms-FINASTERIDE?
These are not all the possible side effects you may have when taking pms-FINASTERIDE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- blood in semen;
- breast swelling and/or tenderness;
- difficulty in achieving an erection that continued after stopping the medication;
- difficulty in achieving an erection;
- less desire to have sex;
- male infertility;
- muscle injury, muscle pain, muscle weakness, abnormal test results (CK elevation);
- problems with ejaculation, such as a decrease in the amount of semen released during sex;
- testicular pain.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Behaviour and mood changes: a sad mood that gets worse or doesn't go away, extreme sadness (depression)		✓	
Self-harm behaviours: injuries from deliberately hurting oneself (self-harm), thought of ending one's life (suicidal ideation)			✓
RARE			
Allergic reactions: hives, itching, rash, and swelling of the lips, tongue, throat and face			✓
Male breast changes: lumps, pain or nipple discharge		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15°C and 30°C and protect from light. Keep blister in the outer carton until all tablets are used.

keep out of reach and sight of children.

If you want more information about pms-FINASTERIDE:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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