

1 PRODUCT NAME

PROPECIA®

finasteride

1 mg film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of PROPECIA contains 1 mg of finasteride.

Excipients with known effect: lactose monohydrate

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

A tan octagonal convex film coated tablet embossed with a P logo on one side and PROPECIA on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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 section 4.6 Fertility, pregnancy and lactation, *Pregnancy*) or children. PROPECIA is not effective in postmenopausal women with androgenetic alopecia.

4.2 Dose and method of 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 from the treatment leads to reversibility of effect within 12 months.

4.3 Contraindications

PROPECIA is contraindicated in the following:

- Use in women when they are or may potentially be pregnant (See section 4.6 Fertility, pregnancy and lactation, *Pregnancy*).
- Hypersensitivity to any component of this product.
- PROPECIA is not indicated for use in women or children.

4.4 Special warnings and precautions for use

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

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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 the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Paediatric Use

PROPECIA is not indicated for use in children.

Use in the Elderly

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

4.5 Interaction with other medicines and other forms of interaction

No medicine interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked medicine metabolising 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, paracetamol, alpha blockers, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Because of the ability of Type II 5 α -reductase inhibitors to inhibit conversion of testosterone to DHT in some tissues, these medicines, including finasteride, may cause abnormalities of the external genitalia of a male foetus 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 male foetuses. 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.

Breast-feeding

PROPECIA is not indicated for use in women.

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

Fertility

Reproduction

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.

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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 do not form copulatory plugs. No medicine-related effect on testes or on mating performance has been seen in rats or rabbits.

Development

Dose-dependent development of hypospadias was observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 µg/kg/day to 100 mg/kg/day (5 to 5,000 times the recommended human dose of 1 mg/day) at an incidence of 3.6 to 100%. 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 µg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day), and decreased anogenital distance when given finasteride in doses ≥ 3 µg/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 5 α -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 5 α -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 foetuses 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 foetal 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 foetuses. In confirmation of the relevance of the rhesus model for human foetal 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 foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose.

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4.7 Effects on ability to drive and use machines

There are no data to suggest that PROPECIA affects the ability to drive or use machinery.

4.8 Undesirable effects

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

Adverse events identified during clinical trials

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, multicentre 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 medicine-related adverse experiences were reported in $\geq 1\%$ of men treated with PROPECIA:

- decreased libido (PROPECIA, 1.8% vs. placebo, 1.3%)
- 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 adverse 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 adverse effects decreased to $\leq 0.3\%$ by the fifth year of treatment with PROPECIA.

Breast Cancer

Finasteride has also been studied in men with prostate disease at 5 times the dosage recommended for the treatment of male pattern hair loss. During the 4-to-6-year placebo and comparator-controlled Medical Therapy of Prostatic Symptoms (MTOPS) study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride 5 mg, but no cases in men not treated with finasteride 5 mg. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men, but no cases in men treated with finasteride 5 mg. During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT) that enrolled 18,882 men, there was 1 case of breast cancer in men treated with placebo. There have been postmarketing reports of male breast cancer with the use of finasteride 1 mg and 5 mg. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown (see section 4.4 Special warnings and precautions for use).

Prostate Cancer

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

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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.

Adverse events identified during postmarketing 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.

Reproductive system and breast disorders:

- sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment;
- breast tenderness and enlargement;
- testicular pain;
- haemospermia
- male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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 effects.

No specific treatment for overdosage with PROPECIA is recommended.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 5 α -reductase inhibitor, ATC code: D11AX10

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

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Mechanism of action

Finasteride is a competitive and specific inhibitor of Type II 5 α -reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($t_{1/2}$ ~ 30 days). 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. Finasteride produces a rapid reduction in serum DHT concentration, reaching significant suppression within 24 hours of dosing.

Hair follicles contain Type II 5 α -reductase. In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT. Administration of finasteride decreases scalp and serum DHT concentrations in these men. In addition, men with a genetic deficiency of Type II 5 α -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 miniaturisation of the scalp hair follicles, leading to reversal of the balding process.

5.2 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 two 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 litres.

There is modest accumulation of finasteride in plasma after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL and was reached 1 to 2 hours post-dose; AUC_(0-24 hr) was 53 ng•hr/mL.

Finasteride has been recovered in the cerebrospinal fluid (CSF) but the medicine 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.

Metabolism

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

Elimination

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

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 more than 70 years

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

Renal impairment

No adjustment in dosage is necessary in non-dialysed patients with renal impairment.

5.3 Preclinical safety data

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).

In mice at a dose of 25 mg/kg/day and in rats at a dose of ≥ 40 mg/kg/day (1,250 and $\geq 2,000$ 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 LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. This suggests the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

No medicine-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).

Mutagenesis

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 μmol) 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. Further, the concentrations (450-550 μmol) 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film-coated tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

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6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Keep container closed and protect from moisture.

6.5 Nature and contents of container

PROPECIA is available in packs of 28 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Organon (New Zealand)
Limited
Level 7, 36 Brandon Street
Wellington 6011
Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

04 December 1997

10 DATE OF REVISION OF THE TEXT

17 August 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Amend sponsor details due to new sponsor address

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