

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

/.../ 1 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 1 mg of finasteride.

Excipient(s) with known effect: lactose monohydrate 87.80 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Brown colour, round shaped film coated tablets with a dimension of 6.6 x 6.8 mm, debossed with 'H' on one side and '36' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

/.../ is indicated for early stages of androgenetic alopecia in men.

/.../ stabilizes the process of the androgenetic alopecia in men 18-41 year of age. Efficacy in bitemporal recession and end-stage hair loss has not been established.

/.../ is **not** indicated for use in women or children and adolescents.

4.2 Posology and method of administration

Posology

The recommended dosage is one 1 mg tablet daily with or without food.

There is no evidence that an increase in dosage will result in increased efficacy.

Efficacy and duration of treatment should continuously be assessed by the treating physician. Generally, three to six months of once daily treatment are required before evidence of stabilization of hair loss can be expected. Continuous use is recommended to sustain benefit. If treatment is stopped, the beneficial effects begin to reverse by six months and return to baseline by 9 to 12 months.

Patients with renal insufficiency

No dosage adjustment is required in patients with renal insufficiency.

No data are available on the concomitant use of finasteride and topical minoxidil in male pattern hair loss.

Method of administration

For oral use only.

The tablet should be swallowed whole and must not be divided or crushed (See section 6.6).

4.3 Contraindications

Contraindicated in women (see section 4.6 and 5.1).

Should not be taken by men who are taking finasteride 5 mg or any other 5 α -reductase inhibitor for benign prostatic hyperplasia or any other condition.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

/.../ must not be used in children / adolescents. There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.

In clinical studies with /.../ 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. Doubling the PSA level in men taking finasteride should be considered before evaluating this test result.

Long-term data on fertility in humans are lacking, and specific studies in subfertile men have not been conducted. The male patients who were planning to father a child were initially excluded from clinical trials. Although, animal studies did not show relevant negative effects on fertility, spontaneous reports of infertility and/or poor seminal quality were received post-marketing. In some of these reports, patients had other risk factors that might have contributed to infertility. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.

The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied.

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.

Mood alterations including depressed mood, depression 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, treatment with finasteride should be discontinued and the patient advised to seek medical advice.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Finasteride is metabolized primarily via, but does not affect the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4 will affect the plasma concentration of finasteride. However, based on established safety margins, any increase due to concomitant use of such inhibitors is unlikely to be of clinical significance.

4.6 Fertility, pregnancy and lactation

Pregnancy

/.../ is contraindicated or use in women due to the risk in pregnancy.

Because of the ability of finasteride to inhibit conversion of testosterone to dihydrotestosterone (DHT). Finasteride may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman (See section 6.6).

Exposure to finasteride - : risk to male foetus

A small amount of finasteride, less than 0.001% of the 1 mg dose per ejaculation, has been detected in the seminal fluid of men taking finasteride. Studies in Rhesus monkeys have indicated that this amount is unlikely to constitute a risk to the developing male foetus.

During continual collection of adverse experiences, post-marketing reports of exposure to finasteride during pregnancy via semen of men taking 1 mg or higher doses have been received for eight live male births, and one retrospectively-reported case concerned an infant with simple hypospadias. Causality cannot be assessed on the basis of this single retrospective report and hypospadias is a relatively common congenital anomaly with an incidence ranging from 0.8 to 8 per 1000 live male births. In addition, a further nine live male births occurred during clinical trials following exposure to finasteride via semen, during pregnancy, and no congenital anomalies have been reported.

Crushed or broken tablets of /.../ should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus. Finasteride tablets are coated to prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

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

4.7 Effects on ability to drive and use machines

There are no data to suggest that /.../ affects the ability to drive or use machines.

4.8 Undesirable effects

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 finasteride and placebo were similar. Discontinuation of therapy due to any clinical adverse experience 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 experiences were reported in $\geq 1\%$ of men treated with finasteride: decreased libido (Finasteride, 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 Finasteride and 0.4% of men treated with placebo. Resolution of these side effects occurred in men who discontinued therapy with Finasteride and in many who continued therapy. The effect of Finasteride on ejaculate volume was measured in a separate study and was not different from that seen with placebo. By the fifth year of treatment with Finasteride, the proportion of patients reporting each of the above side effects decreased to $\leq 0.3\%$.

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 placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of finasteride 5 mg and tumours with Gleason scores of 7-10 is unknown.

The frequencies of undesirable effects are following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

The adverse reactions during clinical trials and/or post-marketing use frequencies of undesirable effects are listed in the table below..

| | |
|---|---|
| Immune system disorders: | <i>Not known:</i> Hypersensitivity reactions, such as rash, pruritus, urticaria and angioedema (including swelling of the lips, tongue, throat and face) |
| Cardiac disorders: | <i>Not known:</i> Palpitation |
| Psychiatric disorders: | <i>Uncommon*:</i> Decreased libido <i>Uncommon:</i> Depression [†] <i>Not known:</i> Anxiety |
| Hepatobiliary disorders: | <i>Not known:</i> Increased hepatic enzymes. |
| Reproductive system and breast disorders: | <i>Uncommon*:</i> Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate) <i>Not known:</i> Breast tenderness and enlargement, Testicular pain, infertility** |

** See section 4.4

* Incidences presented as difference from placebo in clinical studies at Month 12.

† This adverse reaction was identified through post-marketing surveillance but the incidence in randomized controlled Phase III clinical trials (Protocols 087, 089, and 092) was not different between finasteride and placebo.

Drug-related sexual undesirable effects were more common in the finasteride 1 mg-treated men than the placebo-treated men, with frequencies during the first 12 months of 3.8% vs 2.1%, respectively. The incidence of these effects decreased to 0.6% in finasteride 1 mg-treated men over the following four years. Approximately 1% of men in each treatment group discontinued due to drug related sexual adverse experiences in the first 12 months, and the incidence declined thereafter.

In addition, the following have been reported in post-marketing use: persistence of sexual dysfunction (decreased libido, erectile dysfunction and ejaculation disorders) after discontinuation of treatment with Finasteride 1 mg tablets: male breast cancer (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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 (n=71) did not result in dose related side effects.

No specific treatment of overdose with finasteride Tablets 1mg is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatologicals, ATC code: D11 AX10.

Finasteride is a 4-azasteroid, which inhibits human Type 2 5 α -reductase (present within the hair follicles) with greater than 100-fold selectivity over human Type 1 5 α -reductase, and blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT). In men with male pattern hair loss, the balding scalp contains miniaturized hair follicles and increased amounts of DHT. Finasteride inhibits a process responsible for miniaturization of the scalp hair follicles, which can lead to reversal of the balding process.

Studies in men:

The efficacy of Finasteride 1 mg was demonstrated in three studies in 1879 men 18 to 41 years of age with mild to moderate, but not complete, vertex hair loss and frontal/mid-area hair loss. In these studies, hair growth was assessed using four separate measures including hair count, ratings 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 1 mg was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning at 3 to 6 months. While hair improvement measures compared to baseline in men treated with Finasteride 1 mg were generally greatest at 2 years and gradually declined thereafter (e.g., hair count in a representative 5.1 cm² area was increased 88 hairs from baseline at 2 years and 38 hairs from baseline 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, although improvement compared to baseline in men treated with Finasteride 1 mg did not increase further after 2 years, the difference between treatment groups continued to increase throughout the 5 years of the studies. Treatment with Finasteride 1 mg 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 observed in 65% of men treated with Finasteride 1 mg based on hair counts, in 48% based on photographic assessment, and in 77% based on investigator assessment. In contrast, in the placebo group, gradual hair loss over time was observed in 100% of men based on hair counts, in 75% based on photographic assessment, and in 38% based on investigator assessment. In addition, patient self-assessment demonstrated significant increases in hair density, decreases in hair loss, and improvement in appearance of hair after treatment over 5 years with Finasteride 1 mg (see Table below).

In a 12-month study, in men with frontal/mid-area hair loss, hair counts were obtained in a representative 1 cm² area (approximately 1/5 the size of the area sampled in the vertex studies). Hair counts, adjusted to a 5.1 cm² area, increased by 49 hairs (5%) compared to baseline and by 59 hairs (6%) compared to placebo. This study also demonstrated significant improvements in patient self-assessment, investigator assessment, and ratings of photographs of the head by an expert panel of dermatologists.

Two studies of 12 and 24 weeks duration showed that a dose 5-fold the recommended dose (finasteride 5 mg daily) produced a median decrease in ejaculate volume of approximately 0.5 mL (-25%) compared with placebo. This decrease was reversible after discontinuation of treatment. In a study of 48 weeks of duration, finasteride 1 mg daily produced a median decrease in ejaculate volume of 0.3 mL (-11%) compared with a 0.2 mL (-8%) decrease for placebo. No effect was observed on sperm count, motility or morphology. Longer-term data are not available. It has not been feasible to undertake clinical studies which directly elucidate possible negative effects on fertility. However, such effects are judged as very unlikely (see also 5.3 Preclinical safety data).

| Percent of Patients Improved as Assessed by Each of the 4 Measures | | | | | | |
|--|---------------------|---------------|----------------------|--------------|----------------------|-------------|
| | Year 1 [†] | | Year 2 ^{††} | | Year 5 ^{††} | |
| | Finasteride 1 mg | Placebo | Finasteride 1 mg | Placebo | Finasteride 1 mg | Placebo |
| Hair Count | (N=679) 86 | (N=672) 42 | (N=433) 83 | (N=47) 28 | (N=219) 65 | (N=15) 0 |

| | | | | | | |
|--|---------------|---------------|---------------|--------------|---------------|--------------|
| Global Photographic Assessment | (N=720) 48 | (N=709) 7 | (N=508) 66 | (N=55) 7 | (N=279) 48 | (N=16) 6 |
| Investigator Assessment | (N=748) 65 | (N=747) 37 | (N=535) 80 | (N=60) 47 | (N=271) 77 | (N=13) 15 |
| Patient Self-Assessment: Satisfaction with appearance of hair overall | (N=750) 39 | (N=747) 22 | (N=535) 51 | (N=60) 25 | (N=284) 63 | (N=15) 20 |

† Randomization 1:1 Finasteride 1 mg tablets to placebo

†† Randomization 9:1 Finasteride 1 mg tablets to placebo

Studies in women

Lack of efficacy was demonstrated in post-menopausal women with androgenetic alopecia who were treated with finasteride 1 mg for 12 months.

5.2 Pharmacokinetic properties

Absorption

The oral bioavailability of finasteride is approximately 80% and is not affected by food. Maximum finasteride plasma concentrations are reached approximately two hours after dosing and the absorption is complete after six to eight hours.

Distribution

Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 liters (44-96 l).

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 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. Studies in rhesus monkeys showed that this amount is not considered to constitute a risk to the developing male foetus (see 4.6 and 5.3)..

Biotransformation

Finasteride is metabolized primarily via but does not affect the cytochrome P450 3A4 system. Following an oral dose of ¹⁴C-finasteride in man, two metabolites of the drug 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 drug was excreted in the urine and 57 % (51-64 %) of total dose was excreted in the faeces.

Plasma clearance is approximately 165 ml/min (70-279 ml/min).

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours (3-14 hours, in men more than 70 years of age 8 hours (6-15 hours)). These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

Hepatic insufficiency:

The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied.

Renal insufficiency:

In patients with chronic renal impairment, with creatinine clearances ranging from 9-55 ml/min, area under the curve, maximum plasma concentrations, half-life, and protein binding of unchanged finasteride after a single dose of ¹⁴C-finasteride were similar to values obtained in healthy volunteers.

5.3 Preclinical safety data

Mutagenicity/carcinogenicity

Studies on genotoxicity and carcinogenicity have not revealed any hazards for humans.

Reproduction disturbing effect including fertility

The effects on embryonal and foetal development have been studied in rats, rabbits and rhesus monkeys. In rats treated with 5-5,000 times the clinical dose, a dose-related occurrence of hypospadias has been observed in male foetuses. In rhesus monkeys, treatment with oral doses of 2 mg/kg/day has also resulted in external genital abnormalities. Intravenous doses of up to 800 ng/day in rhesus monkeys have not shown any effects in male foetuses. This represents at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day (see 5.2). In the rabbit study the foetuses were not exposed to finasteride during the period critical for genital development.

Neither ejaculation volume, sperm count nor fertility were affected in the rabbit after treatment with 80 mg/kg/day, a dose that in other studies is shown to have pronounced weight lowering effect of accessory sexual glands. In rats treated for 6 and 12 weeks with 80 mg/kg/day (approx. 500 times the clinical exposure) no effect on fertility was observed. After 24-30 weeks treatment some reduced fertility and pronounced weight reduction of prostate and seminal vesicle were seen. All changes were reversible within a 6-week period. The reduced fertility has been shown to be due to impaired seminal plug formation, an effect that has no relevance to man. The development of the newborns and their reproduction capacity at the age of sexual maturation were without remark. After insemination of female rats with epididymis sperms from rats treated for 36 weeks with 80 mg/kg/day no effect was seen on a number of fertility parameters.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Microcrystalline cellulose
Starch pregelatinized (maize)
Sodium starch glycolate (Type A)
Docusate Sodium
Magnesium Stearate

Film coating:

Hypromellose (E464)
Titanium Dioxide (E171)
Talc
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-Aluminium Blister.

Pack sizes: 7, 10, 14, 15, 20, 28, 30, 49, 50, 56, 60, 84, 90, 98, 100, 112, 120, 250, 300, 500 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Crushed or broken tablets of /.../ should not be handled by women when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see section 4.6). /.../ tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]