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PROPECIA Tablets

Merck Sharp & Dhome

1. NAME OF THE MEDICINAL PRODUCT

PROPECIA® 1 mg Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of 'Propecia' contains 1 mg of finasteride as the active ingredient.

3. PHARMACEUTICAL FORM

Film-coated tablet. Tan octagonal, film-coated, convex tablets, marked 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 or children and adolescents.

4.2 Posology and method of administration

The recommended dosage is one 1 mg tablet daily. 'Propecia' may be taken 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 stabilisation 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.

No dosage adjustment is required in patients with renal insufficiency.

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

4.3 Contraindications

'Propecia' is contraindicated for use in women due to the risk in pregnancy (see 4.6 'Pregnancy and lactation') and in patients with hypersensitivity to any component of this product.

'Propecia' is not indicated for use in women or children and adolescents.

'Propecia' should not be taken by men who are taking 'Proscar' (finasteride 5 mg) or any other 5α-reductase inhibitor for benign prostatic hyperplasia or any other condition.

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. This decrease in serum PSA concentrations needs to be considered, if during treatment with 'Propecia', a patient requires a PSA assay. In this case the PSA value should be doubled before making a comparison with the results from untreated men.

Excipients

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

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolising enzyme system. Compounds which have been tested in man have included antipyrine, digoxin, glibenclamide, 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, H_2 antagonists, HMG-CoA reduc-

tase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Use during pregnancy

'Propecia' is contra-indicated for use in women due to the risk in pregnancy.

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

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 'Propecia'. Studies in Rhesus monkeys have indicated that this amount is unlikely to constitute a risk to the developing male foetus (see Section 5.3).

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 'Propecia' 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. 'Propecia' tablets are coated to prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

Use during lactation

'Propecia' is contraindicated for use in lactation.

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 machines.

4.8 Undesirable effects

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, 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 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. The effect of 'Propecia' 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 'Propecia', the proportion of patients reporting each of the above side effects decreased to <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 following undesirable effects have been reported in post-marketing use: ejaculation disorder; breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria and swelling of the lips and face; and testicular pain.

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 side effects.

No specific treatment of overdosage with 'Propecia' is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 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, oestrogenic, anti-oestrogenic, or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen 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 5α-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. Men with a genetic deficiency of type II 5α-reductase do not suffer from male pattern hair loss. Finasteride inhibits a process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process.

Studies in men

Clinical studies were conducted in 1879 men aged 18 to 41 with mild to moderate, but not complete, vertex hair loss and/or frontal/mid-area hair loss. In the two studies in men with vertex hair loss (n=1553), 290 men completed 5 years of treatment with Propecia vs. 16 patients on placebo. In these two studies, efficacy was assessed by the following methods: (i) hair count in a representative 5.1 cm^2 area of scalp, (ii) patient self assessment questionnaire, (iii) investigator assessment using a seven point scale, and (iv) photographic assessment of standardised paired photographs by a blinded expert panel of dermatologists using a seven point scale.

In these 5- year studies men treated with 'Propecia' improved compared to both baseline and placebo beginning as early as 3 months, as determined by both the patient and investigator assessments of efficacy. With regard to hair count, the primary endpoint in these studies, increases compared to baseline were demonstrated starting at 6 months (the earliest time point assessed) through to the end of the study. In men treated with 'Propecia' these increases were greatest at 2 years and gradually declined thereafter to the end of 5 years; whereas hair loss in the placebo group progressively worsened compared to baseline over the entire 5 year period. In 'Propecia' treated patients, a mean increase from baseline of 88 hairs *[p<0.01; 95% CI (77.9, 97.80; n=433]* in the representative 5.1 cm^2 area was observed at 2 years and an increase from baseline of 38 hairs *[p<0.01; 95% CI (20.8, 55.6); n=219]* was observed at 5 years, compared with a decrease from baseline of 50 hairs *[p<0.01; 95% CI (-80.5, -20.6);n=47]* at 2 years and a decrease from baseline of 239 hairs *[p<0.01; 95% CI (-304.4, -173.4); n=15]* at 5 years in patients who received placebo. Standardised photographic assessment of efficacy demonstrated that 48% of men treated with finasteride for 5 years were rated as improved, and an additional 42% were rated as unchanged. This is in comparison to 25% of men treated with placebo for 5 years who were rated as improved or unchanged. These data demonstrate that treatment with 'Propecia' for 5 years resulted in a stabilisation

of the hair loss that occurred in men treated with placebo.

An additional 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, anagen and telogen 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.

Studies in women

Lack of efficacy was demonstrated in post-menopausal women with androgenetic alopecia who were treated with 'Propecia' in a 12 month, placebo-controlled study (n=137). These women did not show any improvement in hair count, patient self-assessment, investigator assessment, or ratings based on standardised photographs, compared with the placebo group.

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 six to eight hours.

Distribution

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

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 postdose; $AUC_{(0\text{-}24hr)}$ 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 small amount of finasteride has also been detected in the seminal fluid of subjects receiving the drug.

Biotransformation

Finasteride is metabolised primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of ^{14}C-finasteride in man, two metabolites of the drug 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 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 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 non-dialysed patients with renal impairment.

5.3 Preclinical safety data

In general, the findings in laboratory animal studies with oral finasteride were related to the pharmacological effects of 5α-reductase inhibition.

Intravenous administration of finasteride to pregnant rhesus monkeys at doses as high as 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This represents at least 750 times the highest estimated exposure of pregnant women to

finasteride from semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (100 times the recommended human dose or approximately 12 million times the highest estimated exposure to finasteride from semen) 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, microcrystalline cellulose E460, pregelatinised maize starch, sodium starch glycollate, docusate sodium, magnesium stearate E572, hypromellose E464, hydroxypropyl cellulose E463, titanium dioxide, talc, yellow iron oxide E172, red iron oxide E172.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Store in original package.

6.5 Nature and contents of container

Aluminium blisters lidded with aluminium foil, containing 28 tablets or 84 tablets.

6.6 Special precautions for disposal and other handling

Crushed or broken tablets of 'Propecia' should not be handled by women when they are or may potentially be pregnant (see 4.6 'Pregnancy and lactation').

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK.

8. MARKETING AUTHORISATION NUMBER

PL 0025/0351

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 September 1999/ 21 July 2005

10. DATE OF REVISION OF THE TEXT

September 2008

LEGAL CATEGORY

POM

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Here above is the latest summary of products characteristics submitted to the Ministry of Health in UAE (November 2008)