SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

PROSCAR® 5 mg Tablet

COMPOSITION

Each PROSCAR 5 mg Tablet contains 5 mg finasteride.

PROSCAR Tablets contain sugar.

PHARMACOLOGICAL CLASSIFICATION

A.21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION

Pharmacodynamic Properties

Finasteride, a synthetic 4-azasteroid compound, is an inhibitor of Type II 5-alpha reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen dihydrotestosterone (DHT).

In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Finasteride reduces circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

Pharmacokinetic Properties

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 the total dose was excreted in the faeces. Two metabolites of finasteride have been identified which possess only a small fraction of the 5-alpha reductase inhibitory activity of finasteride.

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 80 %. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately 2 hours after dosing and the absorption is complete after 6 to 8 hours. Finasteride displays a mean plasma elimination half-life of approximately 6 hours (4 to 12 hours) in subjects 46 to 60 years of age and approximately 8 hours in men 70 years of age and older. Protein binding is approximately 93 %. Plasma clearance and the volume of distribution of finasteride are approximately 165 ml/min and 76 litres, respectively.

Summary of Clinical Studies

Information from a recently completed 7-year placebo-controlled trial that enrolled 18 882 men ≥ 55 years of age, with a normal digital rectal examination and a PSA of ≤ 3,0 ng/ml, may be relevant for men currently being treated with PROSCAR for BPH. At the end of the study, 9 060 men had prostate needle biopsy data available for analysis. In this study, prostate cancer was detected in 803 (18,4 %) men receiving PROSCAR and 1 147 (24,4 %) men receiving placebo (see also **SIDE EFFECTS, Other long-term data**). PROSCAR is not indicated to reduce the risk of developing prostate cancer.

INDICATIONS

PROSCAR 5 mg is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

- Improve urinary flow and improve the symptoms associated with BPH by causing regression of the enlarged prostate.
- Reduce the incidence of acute urinary retention.
- Reduce the incidence of surgery including transurethral resection of the prostate (TURP) and prostatectomy.

In a 4 year double blind, placebo controlled study with 3 040 patients with moderate to severe symptoms of BPH, acute urinary retention and prostatic surgery occurred in 2,8 % and 4,6 % of patients on finasteride 5 mg per day, compared with 6,6 % and 10,1 % of patients on placebo, respectively. The difference from placebo was statistically significant.

From a baseline score of approximately 15 out of a possible total score of 34, based on symptoms of obstruction and irritation, patients randomised to PROSCAR who remained on therapy for 4 years had a mean (± SD) decrease in symptom score of 3,3 (± 5,8) points compared with 1,3 (± 5,6) points in the placebo group. A statistically significant improvement in symptoms was evident at one year in patients treated with PROSCAR vs. placebo (-2,3 vs. -1,6 points).

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Pregnancy and lactation - Use in women when they are or may potentially be pregnant (see **PREGNANCY AND LACTATION**).

PROSCAR 5 mg is not indicated for use in women.

Paediatric use.

WARNINGS AND SPECIAL PRECAUTIONS

General

Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.

Effects on PSA and Prostate Cancer Detection

No clinical benefit has been demonstrated in patients with prostate cancer treated with PROSCAR 5 mg.

Digital rectal examinations as well as other evaluations for prostate cancer are recommended prior to initiating therapy with PROSCAR 5 mg and periodically thereafter. Serum PSA is also used for prostate cancer detection. Generally a baseline S-PSA > 10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for S-PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in S-PSA levels among men with and without prostate cancer. Therefore, in men with BPH, S-PSA values within the normal reference range do not rule out prostate cancer, regardless of treatment with PROSCAR 5 mg. A baseline S-PSA < 4 ng/ml does not exclude prostate cancer.

PROSCAR 5 mg causes a decrease in S-PSA concentrations by approximately 50 % in patients with BPH, even in the presence of prostate cancer. This decrease in S-PSA levels in patients with BPH treated with PROSCAR 5 mg should be considered when evaluating S-PSA data, and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Analysis of S-PSA data from over 3 000 patients in the 4-year, double-blind, placebo-controlled

PROSCAR Long-Term Efficacy and Safety Study (PLESS) confirmed that in typical patients treated with PROSCAR 5 mg for 6 months or more, S-PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the S-PSA assay and maintains its ability to detect prostate cancer.

Patients treated with PROSCAR 5 mg who have a sustained increase in S-PSA levels should be carefully evaluated.

Percent free PSA (free to total PSA ratio) is not significantly decreased by PROSCAR. The ratio of free to total PSA remains constant even under the influence of PROSCAR. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment to its value is necessary.

INTERACTIONS

Effect on levels of S-PSA

Concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When S-PSA laboratory determinations are evaluated, consideration should be given to the fact that S-PSA levels decrease in patients treated with PROSCAR 5 mg. In most patients, a rapid decrease in S-PSA is seen within the first months of therapy, after which time S-PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with PROSCAR 5 mg for 6 months or more, S-PSA values should be doubled for comparison to normal ranges in untreated men.

For clinical interpretation, see **WARNINGS AND SPECIAL PRECAUTIONS**, **Effects on PSA and Prostate Cancer Detection**.

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Medicine Interactions

No medicine interactions of clinical importance have been identified. PROSCAR 5 mg does not appear to significantly affect the cytochrome P450-linked drug metabolising enzyme system.

Compounds which have been tested in man have included propranolol, digoxin, glibenclamide, warfarin, theophylline and antipyrine and no clinically meaningful interactions were found.

Other Concomitant Therapy

Although specific interaction studies were not performed, in clinical studies PROSCAR 5 mg was used concomitantly with ACE inhibitors, paracetamol, acetylsalicylic acid, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

Laboratory Test Findings

No differences in standard laboratory parameters were observed between patients treated with placebo or PROSCAR 5 mg.

PREGNANCY AND LACTATION

PROSCAR 5 mg is contraindicated for use in women when they are or may potentially be pregnant (see **CONTRAINDICATIONS**).

Because of the ability of Type II 5-alpha reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, PROSCAR 5 mg may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

Exposure to PROSCAR 5 mg - Risk to Male Foetus

Women should not handle crushed or broken PROSCAR 5 mg Tablets when they are or may potentially be pregnant because of the possibility of absorption of PROSCAR 5 mg and the subsequent potential risk to male foetus (see **PREGNANCY AND LACTATION**). PROSCAR 5 mg Tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

It is not known whether PROSCAR 5 mg is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

The recommended dosage is one 5 mg tablet daily with or without food.

Although early improvement in symptoms may be seen, a therapeutic trial of 6 to 12 months may be necessary to assess whether a beneficial response has been achieved.

Dosage in Renal Insufficiency

No adjustments in dosage are required in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 ml/min) as pharmacokinetic studies did not indicate any change in the disposition of PROSCAR 5 mg.

Dosage in the Elderly

No adjustment in dosage is required although pharmacokinetic studies indicated the elimination of PROSCAR 5 mg is decreased in patients more than 70 years of age.

SIDE EFFECTS

The following adverse experiences have been reported during clinical trials and/or in post-marketing use:

Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥ 1/10 000, < 1/1 000); Very rare (≤ 1/10 000), including isolated reports.

Reproductive system and breast disorders

Common: Decreased volume of ejaculate, impotence.

Psychiatric disorders

Common: Decreased libido.

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 3 047 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 3 040 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 finasteride 5 mg, and 1 case of breast cancer in men treated with placebo. There have been post-marketing 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.

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).

Psychiatric disorders: Depression, decreased libido that continued after discontinuation of treatment.

Reproductive systems and breast disorders: Breast tenderness and enlargement, testicular pain, haematospermia, sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment, male infertility and/or poor seminal quality. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.

Other Long-Term Data

In a 7-year placebo-controlled trial that enrolled 18 882 healthy men, of whom 9 060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18,4 %) men receiving PROSCAR and 1 147 (24,4 %) men receiving placebo. In the PROSCAR group, 280 (6,4 %) men had prostate cancer with Gleason scores of 7 to 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 PROSCAR group may be explained by a detection bias due to the effect of PROSCAR on prostate volume. Of the total cases of prostate cancer diagnosed in this study, approximately 98 % were classified as intra-capsular (clinical stage T1 or T2) at diagnosis. The relationship

between long-term use of PROSCAR and tumours with Gleason scores of 7 to 10 is unknown.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No specific treatment of overdosage with PROSCAR 5 mg is recommended.

Treatment is symptomatic and supportive.

IDENTIFICATION

PROSCAR 5 mg is an apple-shaped, film-coated blue tablet engraved MSD 72 on the one side and PROSCAR on the other.

PRESENTATION

PROSCAR 5 mg Tablets are available in blister packs of 28 tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C and protect from light. Store in the original packaging.

Women should not handle crushed or broken tablets of PROSCAR 5 mg when they are or may potentially be pregnant (see **CONTRAINDICATIONS** and **PREGNANCY AND LACTATION, Exposure to PROSCAR 5 mg – Risk to Male Foetus**).

Keep out of reach of children.

REGISTRATION NUMBER

27/21.12/0069

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

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1685

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date on the registration certificate: 29 October 1992

Date of the most recent revision: 25 October 2005 (SR-PIN: 31 October 2018)

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