

## **Name of Medicine**

### **PROSCAR<sup>®</sup>**

*(finasteride)*

5mg tablets

## **Presentation**

PROSCAR 5mg tablets are blue, apple shaped, film coated tablets engraved MSD72 on one side and engraved PROSCAR on the other. (Dimensions 7.18mm long x 7.99mm wide.)

## **Indications**

PROSCAR is indicated for the treatment and control of benign prostatic hyperplasia (BPH) and for the prevention of urologic events to;

- Reduce the risk of acute urinary retention
- Reduce the risk of surgery including transurethral resection of the prostate (TURP) and prostatectomy

PROSCAR causes regression of the enlarged prostate, improved urinary flow and improves the symptoms associated with BPH

Patients with enlarged prostate are the appropriate candidates for therapy with PROSCAR.

## **Dosage and Administration**

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

### **Dosage in Renal Insufficiency**

No adjustment in dosage is 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 finasteride.

### **Dosage in the Elderly**

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

## **Contraindications**

PROSCAR is not indicated for use in women or children.

PROSCAR is contraindicated in the following:

- Hypersensitivity to any component of this product.
- Pregnancy - Women who are or may potentially be pregnant (see Warnings and Precautions: Pregnancy and Exposure to Finasteride – Risk to Male Foetus)

## Warnings and 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 yet been demonstrated in patients with prostate cancer treated with PROSCAR. Patients with BPH and elevated prostate-specific antigen (PSA) were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these BPH studies, PROSCAR did not appear to alter the rate of prostate cancer detection and the overall incidence of prostate cancer was not significantly different in patients treated with PROSCAR or placebo.

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

PROSCAR causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH, even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with PROSCAR should be considered when evaluating 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 PSA data from over 3000 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 for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to therapy with PROSCAR.

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.

### Medicine/Laboratory Test Interactions

#### Effect on Levels of PSA

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels decrease in patients treated with PROSCAR. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time 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 for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men. For clinical interpretation, see Warnings and Precautions, Effects on PSA and Prostate Cancer Detection.

## **Pregnancy**

PROSCAR is contraindicated in women who 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, these medicines, 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**

Women should not handle crushed or broken tablets of PROSCAR 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 (see Pregnancy). PROSCAR tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Similarly, small amounts of finasteride have been recovered from the semen in subjects receiving PROSCAR 5mg/day. The amount of finasteride measured in ejaculate was 50 - to 100-fold less than the dose of finasteride (5 micrograms) that had no effect on circulating DHT levels in adult males. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen or discontinue PROSCAR (See Contraindications and Pregnancy).

## **Nursing Mothers**

PROSCAR is not indicated for use in women.

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

## **Paediatric Use**

PROSCAR is not indicated for use in children.

Safety and effectiveness in children have not been established.

## **Animal Toxicology**

The oral LD<sub>50</sub> of finasteride in male and female mice is approximately 500 mg/kg. The oral LD<sub>50</sub> of finasteride in female and male rats is approximately 400 and 1000 mg/kg, respectively.

## **Carcinogenesis and Mutagenesis**

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 (3200 times the recommended human dose of 5 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 (2500 times the recommended human dose of 5 mg/day); no adenomas were seen in mice given 2.5 or 25 mg/kg/day (25 and 250 times the recommended human dose of 5 mg/day, respectively).

In mice at a dose of 25 mg/kg/day and in rats at a dose of  $\geq 40$  mg/kg/day (250 and  $\geq 400$  times the recommended human dose of 5 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. This suggests the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

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 (200 and 450 times the recommended human dose of 5 mg/day, respectively) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (25 times the recommended human dose of 5 mg/day).

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 mmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. Further, the concentrations (450-550 mmol) 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; 2500 times the recommended human dose of 5 mg/day).

### **Reproductive Studies**

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (800 times the recommended human dose of 5 mg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen.

In sexually mature male 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 drug-related effect on testes or on mating performance has been seen in rats or rabbits.

### **Developmental Studies**

Dose-dependent development of hypospadias was observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 mcg/kg/day to 100 mg/kg/day (1 to 1000 times the recommended human dose of 5 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  $\geq 30$  mcg/kg/day ( $\geq 30\%$  of the recommended human dose of 5 mg/day), and decreased anogenital distance when given finasteride in doses  $\geq 3$  mcg/kg/day ( $\geq 3\%$  of the recommended human dose of 5 mg/day). The critical period during which these effects can be induced has been defined in rats as days 16-17 of gestation.

The changes described above are expected pharmacological effects of Type II  $5\alpha$ -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 $\alpha$ -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 results in slightly decreased fertility in first generation male offspring ( 3 mg/kg/day; 30 times the recommended human dose of 5 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; 800 times the recommended human dose of 5 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 (1000 times the recommended human dose of 5 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 60 to 120 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5 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; 20 times the recommended human dose of 5 mg/day or approximately 1-2 million times the highest estimated exposure to finasteride from semen of men taking 5 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.

## Adverse Effects

PROSCAR is well tolerated.

In PLESS, 1524 patients treated with PROSCAR 5 mg daily and 1516 patients treated with placebo were evaluated for safety over a period of 4 years. 4.9% (74 patients) were discontinued from treatment due to adverse effects associated with PROSCAR compared with 3.3% (50 patients) treated with placebo. 3.7% (57 patients) treated with PROSCAR and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse effects related to sexual function, which were the most frequently reported adverse effects.

The only clinical adverse reactions considered possibly, probably or definitely medicine related by the investigator, for which the incidence on PROSCAR was  $\geq 1\%$  and greater than placebo over the four years of the study were those related to sexual function, breast complaints and rash. In the first year of the study, impotence was reported in 8.1% of patients treated with PROSCAR vs 3.7% of those treated with placebo; decreased libido was reported in 6.4 vs 3.4% and ejaculation disorder in 0.8 vs 0.1% respectively. In years 2-4 of the study there was no significant difference between treatment groups in the incidences of these three effects. The cumulative incidences in years 2-4 were; impotence (5.1% on PROSCAR 5.1% on placebo); decreased libido (2.6%,2.6%) and ejaculation disorder (0.2%,0.1%). In year one, decreased volume of ejaculate was reported in 3.7 and 0.8% of patients on PROSCAR and placebo respectively; in years 2-4 the cumulative incidence was 1.5% on PROSCAR and 0.5% on placebo. In year 1, breast enlargement (0.5%,0.1%), breast tenderness (0.4%,0.1%) and rash (0.5%,0.2%) were also reported. In years 2-4 the cumulative incidences were; breast enlargement (1.8%,1.1%); breast tenderness (0.7%,0.3%); and rash (0.5%,0.1%).

The adverse experience profile in the 1-year, placebo-controlled, Phase III studies and the 5-year extensions, including 853 patients treated for 5-6 years, was similar to that reported in years 2-4 in PLESS. There is no evidence of increased adverse experiences with increased duration of treatment with PROSCAR. The incidence of new medicine related sexual adverse experiences decreased with duration of treatment.

### **Other Long Term Data**

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 PROSCAR and 1147 (24.4%) men receiving placebo. In the PROSCAR 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 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 intracapsular (clinical stage T1 or T2) at diagnosis. The clinical significance of the Gleason 7-10 data is unknown.

### **Post Marketing Experience**

The following additional adverse effects have been reported in post-marketing experience:

- hypersensitivity reactions, including pruritus, urticaria and swelling of the lips and face.
- testicular pain

### **Laboratory Test Findings**

When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels are decreased in patients treated with PROSCAR (See Warnings and Precautions).

No other difference in standard laboratory parameters was observed between patients treated with placebo or PROSCAR.

### **Interactions**

No medicine interactions of clinical importance have been identified. PROSCAR does not appear to affect significantly the cytochrome P450-linked medicine metabolising enzyme system. Compounds which have been tested in man have included propranolol, digoxin, glyburide, 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 was used concomitantly with ACE-inhibitors, acetaminophen, acetylsalicylic acid, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H<sub>2</sub> antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory medicines (NSAIDs), quinolones, and benzodiazepines without evidence of clinically significant adverse interactions.

### **Overdosage**

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

No specific treatment of overdosage with PROSCAR is recommended.

## Actions

PROSCAR (finasteride, MSD) a synthetic 4-azasteroid compound, is a specific 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 dependant upon the conversion of testosterone to DHT within the prostate, PROSCAR is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

In the PROSCAR Long-Term Efficacy and Safety Study (PLESS), the effect of therapy with PROSCAR on BPH-related urologic events (surgical intervention [e.g. transurethral resection of the prostate and prostatectomy] or acute urinary retention requiring catheterisation) was assessed over a four year period in 3016 patients with moderate or severe symptoms of BPH. In this double blind, randomised, placebo-controlled, multicentre study, treatment with PROSCAR decreased the risk of total urological events by 51% and was also associated with a marked and sustained regression in prostate volume, and a sustained increase in maximum urinary flow rate and improvement in symptoms.

## Pharmacokinetics

Following an oral dose of <sup>14</sup>C-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. In this study, two metabolites of finasteride were 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 two hours after dosing and the absorption is complete after six to eight hours. Finasteride displays a mean plasma elimination half-life of six hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution of finasteride are approximately 165 mL/min and 76 litres, respectively.

A multiple dose study demonstrated a slow accumulation of small amounts of finasteride over time. After daily dosing of 5 mg/day, steady-state trough plasma concentrations of finasteride are estimated to be 8-10 ng/mL and remained stable over time.

The elimination rate of finasteride is somewhat decreased in the elderly. As subjects advance in age, half-life is prolonged from a mean half-life of approximately 6 hours in men 18-60 years of age to 8 hours in men more than 70 years of age. This finding is of no clinical significance and hence, a reduction in dosage is not warranted.

In patients with chronic renal impairment whose creatinine clearance ranged from 9 to 55 mL/min, the disposition of a single dose of <sup>14</sup>C-finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. No adjustment in dosage is necessary in non-dialysed patients with renal impairment.

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

subjects receiving 5 mg/day PROSCAR. The amount of finasteride in the seminal fluid was 50- to 100-fold less than the dose of finasteride (5 mcg) that had no effect on circulating DHT levels in adult males.

## Pharmaceutical Precautions

Store below 30°C (86°F) and protect from light.

Women should not handle crushed or broken tablets of PROSCAR when they are or may potentially be pregnant (see Warnings and Precautions: Pregnancy and Exposure to Finasteride – Risk to Male Foetus).

## Medicine Classification

Prescription Medicine.

## Package Quantities

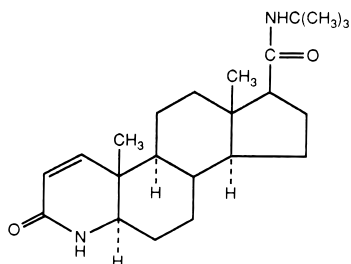
PROSCAR is available in blister platforms containing 15 tablets. (Two platforms per pack.)

## Further Information

### Chemistry

Tablets PROSCAR contains finasteride, which is described chemically as: N-(1,1-dimethylethyl)-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide.

The empirical formula is C<sub>23</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub> and the molecular weight is 372.55. The structural formula is:



Finasteride is a white, crystalline solid. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water.

## Name and Address

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## Date of Preparation

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