PHYSICIANS CIRCULAR

Tablets

PROSCAR®
(finasteride, MSD)

PROSCAR (finasteride, MSD), a synthetic 4-azasteroid compound, is a specific inhibitor of Type II 5α-reductase, an intracellular enzyme which metabolizes 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. 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., transurethal resection of the prostate and prostatectomy] or acute urinary retention requiring catheterization) was assessed over a 4-year period in 3016 patients with moderate to severe symptoms of BPH. In this double-blind, randomized, placebo-controlled multicenter study, treatment with PROSCAR reduced the risk of total urologic 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.

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, improves urinary flow and improves the symptoms associated with BPH.

Patients with an 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.

PROSCAR can be administered alone or in combination with the alpha-blocker doxazosin.

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 - Use in women when they are or may potentially be pregnant (See PRECAUTIONS: PREGNANCY and EXPOSURE TO FINASTERIDE - RISK TO MALE FETUS).

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.

DRUG/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 stabilize to a new baseline. The posttreatment 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 PRECAUTIONS: EFFECTS ON PSA AND PROSTATE CANCER DETECTION.

PREGNANCY

PROSCAR is contraindicated for use in women when they are or may potentially be pregnant (See CONTRAINDICATIONS).

Because of the ability of Type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman.

EXPOSURE TO FINASTERIDE - RISK TO MALE FETUS

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 fetus (see PRECAUTIONS: 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.

NURSING MOTHERS

PROSCAR is not indicated for use in women.

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

PEDIATRIC USE

PROSCAR is not indicated for use in children.

Safety and effectiveness in children have not been established.

DRUG INTERACTIONS

No drug interactions of clinical importance have been identified. PROSCAR does not appear to affect significantly the cytochrome P450-linked drug metabolizing 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_2 antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDS), quinolones, and benzodiazepines without evidence of clinically significant adverse interactions.

SIDE 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 side 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 side effects related to sexual function, which were the most frequently reported side effects.

The only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on PROSCAR was ≥1% and greater than placebo over the 4 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 1, 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 drug-related sexual adverse experiences decreased with duration of treatment.

MEDICAL THERAPY OF PROSTATIC SYMPTOMS (MTOPS)

The MTOPS study compared finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder in patients receiving combination therapy was comparable to the sum of incidences of this adverse experience for the two monotherapies.

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 relationship between long-term use of PROSCAR and tumors with Gleason scores of 7-10 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 PRECAUTIONS).

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

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.

AVAILABILITY

Tab. PROSCAR® (finasteride, MSD) is available as 5 mg (1 X 14's) blister packs

STORAGE AND HANDLING

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 CONTRAINDICATIONS, PRECAUTIONS: PREGNANCY and EXPOSURE TO FINASTERIDE - RISK TO MALE FETUS).