LOCAL PRODUCT CIRCULAR

Tablets

PROSCAR®

(finasteride)

PROSCAR® (finasteride), 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.

PROSCAR administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed 4 point increase in AUA symptom score).

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 - 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. 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 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 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 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.

SPECIAL PRECAUTION

Urethral stricture, infection, cancer, hypotonic bladder and other neurogenic disorders should be excluded before treatment with finasteride is started.

Caution is advised in treating patients with hepatic dysfunction since the drug is extensively metabolised in the liver.

Breast cancer in men
Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and in 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.

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 decreases with duration of treatment.

In addition, the following has been reported in clinical trials and post-marketing use; male breast cancer (see PRECAUTION).

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 clinical significance of the Gleason 7-10 data is unknown. 5-alpha reductase inhibitors may increase the risk of development of high grade prostate cancer. Whether the effect of 5α -reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

BREAST CANCER

During the 4- to 6-year placebo- and comparator-controlled MTOPS study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men but no cases in men treated with finasteride. 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, and 1 case

of breast cancer in men treated with placebo. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

POSTMARKETING EXPERIENCE

The following additional adverse effects have been reported in postmarketing experience with PROSCAR and/or finasteride at lower doses. 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 pruritus, urticaria and angioedema (including swelling of the lips, tongue, throat and face).
Psychiatric disorders: depression; suicidal ideation; decreased libido that continued after discontinuation of treatment.
Reproductive system and breast disorders: sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment; testicular pain; hematospermia; male breast cancer; male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

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.

CLINICAL STUDIES

The data from the studies described below, showing reduced risk of acute urinary retention and surgery, improvement in BPH-related symptoms, increased maximum urinary flow rates, and decreasing prostate volume, suggest that PROSCAR reverses the progression of BPH in men with an enlarged prostate.

PROSCAR 5 mg/day was initially evaluated in patients with symptoms of BPH and enlarged prostates by digital rectal examination in two 1-year, placebo-controlled, randomized, double-blind,

Phase III studies and their 5-year open extensions. Of 536 patients originally randomized to receive PROSCAR 5 mg/day, 234 completed an additional 5 years of therapy and were available for analysis. The efficacy parameters were symptom score, maximum urinary flow rate, and prostate volume.

PROSCAR was further evaluated in the PROSCAR Long-Term Efficacy and Safety Study (PLESS), a double-blind, randomized, placebo-controlled, 4-year multicenter study. In this study, the effect of therapy with PROSCAR 5 mg/day on symptoms of BPH and BPH-related urologic events (surgical intervention [e.g., transurethral resection of the prostate and prostatectomy] or acute urinary retention requiring catheterization) was assessed. 3040 patients between the ages of 45 and 78, with moderate to severe symptoms of BPH and an enlarged prostate upon digital rectal examination, were randomized into the study (1524 to finasteride, 1516 to placebo) and 3016 patients were evaluable for efficacy. 1883 patients completed the 4-year study (1000 in the finasteride group, 883 in the placebo group). Maximum urinary flow rate and prostate volume were also evaluated.

EFFECT ON ACUTE URINARY RETENTION AND THE NEED FOR SURGERY

In the 4-year PLESS study, surgery or acute urinary retention requiring catheterization occurred in 13.2% of the patients taking placebo compared with 6.6% of the patients taking PROSCAR, representing a 51% reduction in risk for surgery or acute urinary retention over 4 years. PROSCAR reduced the risk of surgery by 55% (10.1% for placebo vs. 4.6% for PROSCAR) and reduced the risk of acute urinary retention by 57% (6.6% for placebo vs. 2.8% for PROSCAR). The reduction in risk was evident between treatment groups at first evaluation (4 months) and was maintained throughout the 4-year study (see Figures 1 and 2). Table 1 below shows the rates of occurrence and risk reduction of urologic events during the study.

Figure 1
Percent of Patients Having Surgery for BPH, Including TURP

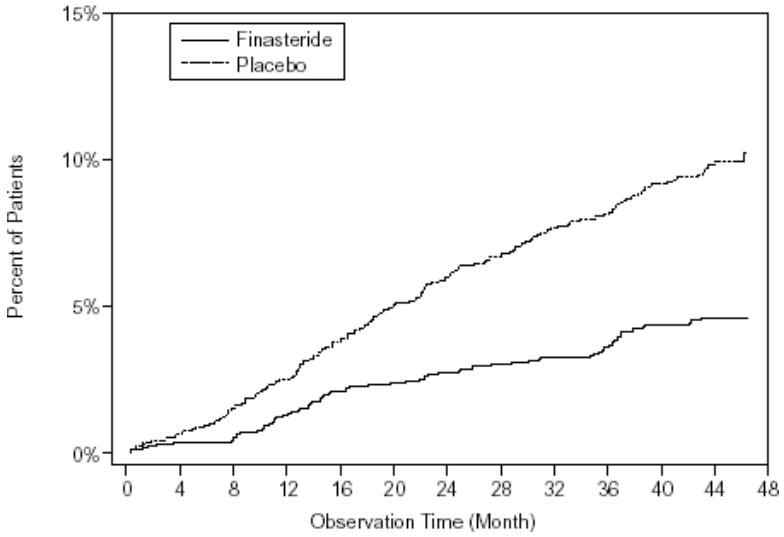


Figure 2
Percent of Patients Developing Acute Urinary Retention
(Spontaneous and Precipitated)

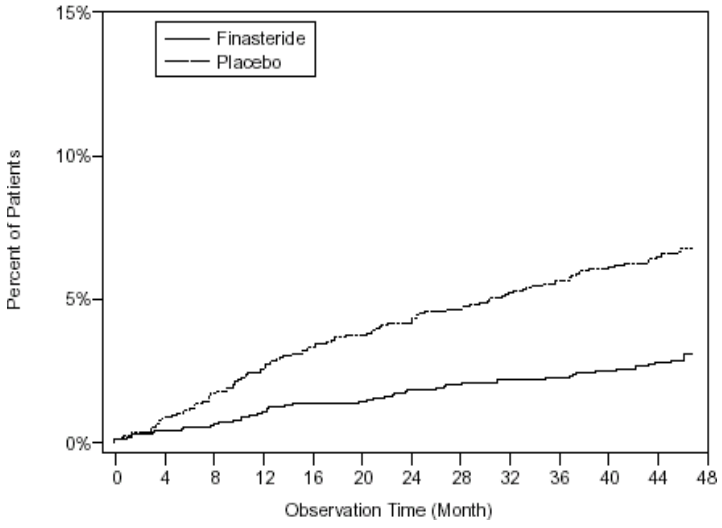


Table 1 RATES OF UROLOGIC EVENTS AND RISK REDUCTION BY PROSCAR OVER 4 YEARS			
Urologic Events	Percent of Patients		Risk Reduction
	Placebo (n = 1503)	Finasteride 5 mg (n = 1513)	
Surgery or Acute Urinary Retention	13.2%	6.6%	51%*
Surgery†	10.1%	4.6%	55%*
TURP	8.3%	4.2%	49%*
Acute Urinary Retention	6.6%	2.8%	57%*

† BPH-related surgery

* $p<0.001$

EFFECT ON SYMPTOM SCORE

In the two 1-year, Phase III studies, mean total symptom scores decreased from baseline as early as week 2. Compared with placebo, a significant improvement in symptoms was observed by months 7 and 10 in these studies. Although an early improvement in urinary symptoms was seen in some patients, a therapeutic trial of at least 6 months was generally necessary to assess whether a beneficial response in symptom relief had been achieved. The improvement in BPH symptoms was maintained through the first year and throughout an additional 5 years of extension studies.

Patients in the 4-year PLESS study had moderate to severe symptoms at baseline (mean of approximately 15 points on a 0-34 point scale). In the patients who remained on therapy for the duration of the 4-year study, PROSCAR improved the symptom score by 3.3 points compared with 1.3 points in the placebo group ($p<0.001$). An improvement in symptom score was evident at 1 year in patients treated with PROSCAR, and this improvement continued through year 4. Symptom scores improved in patients treated with placebo in the first year but worsened thereafter. Patients

with moderate to severe symptoms at baseline tended to have the greatest improvement in symptom score.

EFFECT ON MAXIMUM URINARY FLOW RATE

In the two 1-year, Phase III studies, maximum urinary flow rate was significantly increased compared with baseline by week 2. Compared with placebo, a significant increase in maximum urinary flow rate was observed by months 4 and 7 in these studies. This effect was maintained through the first year and throughout an additional 5 years of extension studies.

In the 4-year PLESS study, there was a clear separation between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4, which was maintained throughout the study. Mean maximum urinary flow rate at baseline was approximately 11 mL/sec in both treatment groups. In the patients who remained on therapy for the duration of the study and had evaluable urinary flow data, PROSCAR increased maximum urinary flow rate by 1.9 mL/sec compared with 0.2 mL/sec in the placebo group.

EFFECT ON PROSTATE VOLUME

In the two 1-year, Phase III studies, mean prostate volume at baseline ranged between 40-50 cc. In both studies, prostate volume was significantly reduced compared with baseline and placebo at first evaluation (3 months). This effect was maintained through the first year and throughout an additional 5 years of extension studies.

In the 4-year PLESS study, prostate volume was assessed yearly by magnetic resonance imaging (MRI) in a subset of patients (n=284). In patients treated with PROSCAR, prostate volume was reduced compared with both baseline and placebo throughout the 4-year study. Of the patients in the MRI subset who remained on therapy for the duration of the study, PROSCAR decreased prostate volume by 17.9% (from 55.9 cc at baseline to 45.8 cc at 4 years) compared with an increase of 14.1% (from 51.3 cc to 58.5 cc) in the placebo group ($p<0.001$).

PROSTATE VOLUME AS A PREDICTOR OF THERAPEUTIC RESPONSE

A meta-analysis combining 1-year data from seven double-blind, placebo-controlled studies of similar design, including 4491 patients with symptomatic BPH, demonstrated that, in patients treated with PROSCAR, the magnitude of symptom response and degree of improvement in

maximum urinary flow rate were greater in patients with an enlarged prostate (approximately 40 cc and greater) at baseline.

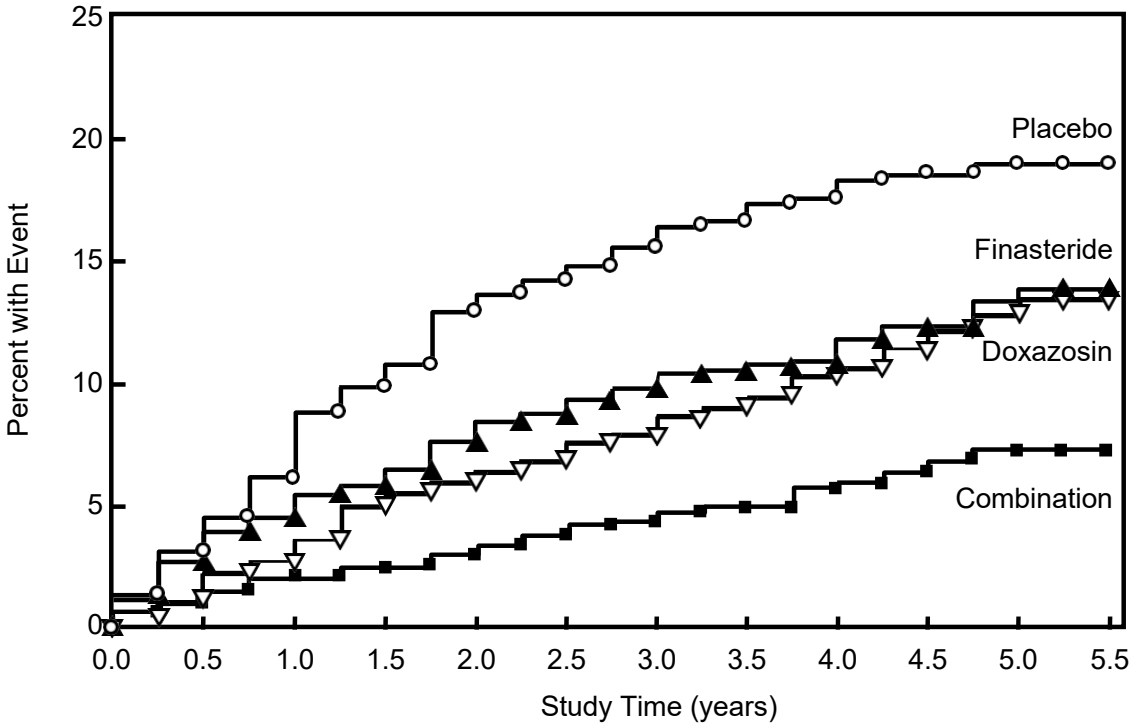
MEDICAL THERAPY OF PROSTATIC SYMPTOMS

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a double-blind, randomized, placebo-controlled, multicenter, 4- to 6- year study (average 5 years) in 3047 men with symptomatic BPH, who were randomized to receive finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day*** (n=756), the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*** (n=786), or placebo (n=737). The primary endpoint was time from randomization to clinical progression of BPH, defined as the first occurrence of any of the following events: a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency (creatinine rise), recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34, 39, and 67%, respectively. Combination therapy reduced the risk of clinical progression of BPH to a significantly greater extent than either finasteride or doxazosin alone, which were not significantly different from each other (see Figure 3). The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30, 46, and 64% in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67, 31, and 79% in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo. Small cumulative numbers of events of renal insufficiency, urinary tract infection, and incontinence were reported and were of limited contribution to the primary endpoint of BPH progression.

Figure 3

Cumulative Incidence of Clinical Progression of BPH by Treatment Group

***Titrated from 1 mg to 4 or 8 mg over a 3-week period



Secondary outcomes measured in MTOPS included the impact of treatment on BPH-related invasive therapy, symptom score, maximum urinary flow, and prostate volume. The risk of requiring BPH-related invasive therapy was reduced by 64, 3, and 67% in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo. All three active treatment groups showed significant improvement in symptom score compared to placebo, and combination therapy was superior to both monotherapy treatments. The effect of combination therapy and doxazosin monotherapy on maximum urinary flow was superior to that of finasteride and placebo. Finasteride and combination treatment decreased prostate volume, whereas, prostate volume increased in men treated with doxazosin or placebo.

The results of MTOPS confirm the findings of the 4-year placebo-controlled study PLESS that treatment with finasteride reduces the risk of acute urinary retention and the need for BPH-related surgery. The results of MTOPS further demonstrate that the combination of finasteride and doxazosin reduces the risk of BPH progression to a significantly greater extent than either therapy administered alone.

CLINICAL PHARMACOLOGY

Benign prostatic hyperplasia (BPH) occurs in the majority of men over the age of 50 and its prevalence increases with age. Epidemiologic studies suggest that enlargement of the prostate gland is associated with a 3-fold increase in the risk of acute urinary retention and prostate surgery. Men with enlarged prostates are also 3 times more likely to have moderate to severe urinary symptoms or a decrease in urinary flow than men with smaller prostates.

The development and enlargement of the prostate gland and subsequent BPH is dependent upon the potent androgen, dihydrotestosterone (DHT). Testosterone, secreted by the testes and adrenal glands, is rapidly converted to DHT by Type II 5α -reductase predominantly in the prostate gland, liver, and skin where it is then preferentially bound to the cell nucleus in those tissues.

Finasteride is a competitive inhibitor of human Type II 5α -reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($t_{1/2}$ ~30 days). *In vitro* and *in vivo*, finasteride has been demonstrated to be a specific Type II 5α -reductase inhibitor, and has no affinity for the androgen receptor.

A single 5 mg dose of finasteride produced a rapid reduction in the serum concentration of DHT, with the maximum effect observed after 8 hours. While plasma levels of finasteride varied over 24 hours, serum DHT levels remained constant during this period, indicating that plasma concentrations of drug do not directly correlate with the plasma concentrations of DHT.

In patients with BPH, finasteride, given for 4 years at a dose of 5 mg/day, was shown to reduce circulating DHT concentrations by approximately 70% and was associated with a median reduction in prostate volume of approximately 20%. Additionally, PSA was reduced approximately 50% from baseline values, suggesting a reduction in prostate epithelial cell growth. Suppression of DHT levels and regression of the hyperplastic prostate with the associated decrease in PSA levels have been maintained in studies of up to 4 years. In these studies, circulating levels of testosterone were increased by approximately 10-20% yet remained within the physiologic range.

When PROSCAR was given for 7-10 days to patients scheduled for prostatectomy, the drug caused a decrease in intraprostatic DHT of approximately 80%. Intraprostatic concentrations of testosterone were increased up to 10 times over pre-treatment levels.

In healthy volunteers treated with PROSCAR for 14 days, discontinuation of therapy resulted in a return of DHT values to pretreatment levels within approximately 2 weeks. In patients treated for

three months, prostate volume, which declined by approximately 20%, returned to close to baseline value after approximately three months of discontinuation of therapy.

Finasteride had no effect compared to placebo on circulating levels of cortisol, estradiol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins and triglycerides) or bone mineral density. An increase of approximately 15% in luteinizing hormone (LH) and 9% in follicle-stimulating hormone (FSH) was observed in patients treated for 12 months; however, these levels remained well within the physiologic range. Gonadotropin-releasing hormone (GnRH) stimulated levels of LH and FSH were not altered, indicating that regulatory control of the pituitary-testicular axis was not affected. Treatment with PROSCAR for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration, motility, morphology, or pH. A 0.6 mL median decrease in ejaculate volume, with a concomitant reduction in total sperm per ejaculate, was observed. These parameters remained within the normal range, and were reversible upon discontinuation of therapy.

Finasteride appeared to inhibit both C_{19} and C_{21} steroid metabolism and hence appeared to have an inhibitory effect on both hepatic and peripheral Type II 5α -reductase activity. The serum DHT metabolites androstenediol glucuronide and androsterone glucuronide were also significantly reduced. This metabolic pattern is similar to that observed in individuals with a genetic deficiency of Type II 5α -reductase who have markedly decreased levels of DHT and small prostates, and who do not develop BPH. These individuals have urogenital defects at birth and biochemical abnormalities but have no other clinically important disorders as a consequence of Type II 5α -reductase deficiency.

PHARMACOKINETICS

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 feces. In this study, two metabolites of finasteride were identified which possess only a small fraction of the 5α -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 liters, 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 ^{14}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 feces. It therefore appears that fecal excretion increases commensurate to the decrease in urinary excretion of metabolites. No adjustment in dosage is necessary in non-dialyzed 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 drug 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 (5µg) that had no effect on circulating DHT levels in adult males.

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

Available in blister packs of 15’ s & 30’ s.

Not all pack sizes may be marketed.

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

APPEARANCE

A blue, apple shaped film coated tablet engraved MSD 72 on one side and PROSCAR on the other side.

SHELF LIFE

Please refer to the expiry date on the outer carton.

MANUFACTURER

AIAC International Pharma, LLC
Road #2, Kilometer 60.3, Sabana Hoyos
Arecibo, Puerto Rico 00688, U.S.A.

PRODUCT REGISTRATION HOLDER

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