PRODUCT MONOGRAPH

[Pr]Accel-Finasteride Tablets USP
5 mg

finasteride

Film-coated Tablets 5 mg

Type II 5α-reductase inhibitor

Accel Pharma Inc.
99 Place Frontenac
Pointe-Claire, QC, H9R 4Z7
Canada

DATE OF PREPARATION:
January 28, 2013

Submission Control No: 161619

TABLE OF CONTENTS

[Pr]Accel-Finasteride Tablets USP
5 mg

finasteride

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
oral	Film-coated Tablet / 5 mg	*Lactose monohydrate, Sodium Starch Glycolate* *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

- Accel-Finasteride Tablets USP is a Type II 5α-reductase inhibitor, indicated as monotherapy 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.
- Accel-Finasteride Tablets USP causes regression of the enlarged prostate, improves urinary flow and improves the symptoms associated with BPH.

Limitations of Use

- Accel-Finasteride Tablets USP is not approved for the prevention of prostate cancer.

Patients with an enlarged prostate are the appropriate candidates for therapy with Accel-Finasteride Tablets USP.

CONTRAINDICATIONS

Accel-Finasteride Tablets USP is not indicated for use in women or children.

Accel-Finasteride Tablets USP is contraindicated in the following:

- Pregnant Women - Use in women when they are or may potentially be pregnant (see WARNINGS and PRECAUTIONS, Exposure to Finasteride - Risk to Male Fetus);
- Hypersensitivity to any component of this product.

WARNINGS AND PRECAUTIONS

General

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

Accel-Finasteride Tablets USP is not indicated for those patients who are candidates for immediate surgery.

No studies have been conducted to determine if finasteride can be used for the control of prostatic hyperplasia in asymptomatic patients.

The long term (>10 years) beneficial and adverse effects of finasteride have not yet been established.

Prior to treatment with Accel-Finasteride Tablets USP, the patient should undergo a thorough urological evaluation to determine the severity of the condition, and to exclude the need for immediate surgery or the possibility of carcinoma of the prostate. Periodic follow-up evaluations should be performed to determine whether a clinical response has occurred.

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

Effects on PSA and Prostate Cancer Detection

In clinical studies, finasteride reduced serum PSA concentration by approximately 50% within six months of treatment. This decrease is predictable over the entire range of PSA values in patients with symptomatic BPH, although it may vary in individuals.

For interpretation of serial PSAs in men taking finasteride, a new PSA baseline should be established at least six months after starting treatment and PSA monitored periodically thereafter. Any confirmed increase from the lowest PSA value while on finasteride may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance with finasteride therapy may also affect PSA test results. To interpret an isolated PSA value in patients treated with finasteride for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. These adjustments preserve the utility of PSA to detect prostate cancer in men treated with finasteride.

Finasteride may also cause decreases in serum PSA in the presence of prostate cancer. The ratio of free to total PSA (percent free PSA) remains constant even under the influence of finasteride. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing finasteride therapy, no adjustment to its value appears necessary.

Increased Risk of High-Grade Prostate Cancer

Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). (See INDICATIONS AND CLINICAL USE and ADVERSE REACTIONS) Similar results were observed in a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride, AVODART*) (1% dutasteride vs 0.5% placebo). 5α-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.

Prior to initiating therapy with finasteride, appropriate evaluation should be conducted to rule out other urological conditions, including prostate cancer that might mimic BPH.

Special Populations

Pregnant and Nursing Women:
Accel-Finasteride Tablets USP 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 such as finasteride to inhibit conversion of testosterone to dihydrotestosterone, finasteride may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman. It is not known whether finasteride is excreted in human milk. In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring. Therefore, if this drug is used during pregnancy or if pregnancy occurs while taking or exposed to this drug, the pregnant woman should be apprised of the potential hazard to the male fetus (see TOXICOLOGY – Developmental Studies).

Exposure to Finasteride – Risk to Male Fetus:
Women should not handle crushed or broken Accel-Finasteride Tablets USP 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 WARNINGS AND PRECAUTIONS, Pregnant and Nursing Women). Accel-Finasteride Tablets USP are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Pediatrics: Accel-Finasteride Tablets USP is not indicated for use in children. Safety and effectiveness in children have not been established.

Monitoring and Laboratory Tests

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 Accel-Finasteride Tablets USP.

* All other trademarks are the property of their respective owners.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Accel-Finasteride Tablets USP is well tolerated.

Clinical Trial Adverse Drug Reactions

In Finasteride Long-Term Efficacy and Safety Study, 1524 patients treated with finasteride 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 finasteride compared with 3.3% (50 patients) treated with placebo. 3.7% (57 patients) treated with finasteride 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.

Table 1 presents the only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on finasteride was ≥ 1% and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido, and ejaculation disorder.

Table 1 Drug-Related Adverse Experiences

	Treatment	Year 1 (%)	Year 2,3 and 4* (%)
Impotence	Placebo	3.7	5.1
	Finasteride	8.1	5.1
Decreased libido	Placebo	3.4	2.6
	Finasteride	6.4	2.6
Decreased volume of ejaculate	Placebo	0.8	0.5
	Finasteride	3.7	1.5
Ejaculation disorder	Placebo	0.1	0.1
	Finasteride	0.8	0.2
Breast enlargement	Placebo	0.1	1.1
	Finasteride	0.5	1.8
Breast tenderness	Placebo	0.1	0.3
	Finasteride	0.14	0.7
Rash	Placebo	0.2	0.1
	Finasteride	0.5	0.5

* Combined years 2-4

The adverse experience profile in the one-year, placebo-controlled, Phase III studies and the five-year extensions, including 853 patients treated for 5 to 6 years, was similar to that reported in years 2-4 in

Finasteride Long-Term Efficacy and Safety Study. There is no evidence of increased adverse experiences with increased duration of treatment with finasteride. The incidence of new drug related sexual adverse experiences decreased with duration of treatment.

Other Long Term Data

High-Grade Prostate Cancer

The PCPT trial was a 7-year randomized, double-blind, placebo-controlled trial that enrolled 18,882 men ≥55 years of age with a normal digital rectal examination and a PSA ≤ 3.0 ng/mL. Men received either finasteride 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams. Biopsies were performed for elevated PSA, an abnormal digital rectal exam, or the end of study. The incidence of Gleason score 8-10 prostate cancer was higher in men treated with finasteride (1.8%) than in those treated with placebo (1.1%) (See INDICATIONS AND CLINICAL USE and WARNINGS AND PRECAUTIONS).

In a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride, AVODART[†]), similar results for Gleason score 8-10 prostate cancer were observed (1% dutasteride vs 0.5% placebo).

No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride.

Laboratory Tests

When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels are decreased in patients treated with finasteride (see WARNINGS AND PRECAUTIONS, Effects on PSA and Prostate Cancer Detection).

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 finasteride 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.

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

Post-Market Adverse Drug Reactions

The following additional adverse reactions have been reported in post-marketing experience: with finasteride 5 mg 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, including pruritus, urticaria and swelling of the lips and face;

[†] All other trademarks are the property of their respective owner(s).

Psychiatric Disorders: depression, decreased libido that continued after discontinuation of treatment;

Reproductive system and breast disorders: male breast cancer, testicular pain; erectile dysfunction that continued after discontinuation of treatment; male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

DRUG INTERACTIONS

Overview

No drug interactions of clinical importance have been identified. Finasteride, at prescribed doses, 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. However, patients on medications with narrow therapeutic indices, such as phenytoin, should be carefully monitored when treatment with finasteride is initiated.

Drug-Drug Interactions

Although specific interaction studies were not performed, in clinical studies finasteride was used concomitantly with ACE-inhibitors, acetaminophen, acetylsalicylic acid, alpha-blockers, betablockers, 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Accel-Finasteride Tablets USP as monotherapy 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.
- Accel-Finasteride Tablets USP causes regression of the enlarged prostate, improves urinary flow and improves the symptoms associated with BPH.

Recommended Dose and Dosage Adjustment

The recommended dosage of Accel-Finasteride Tablets USP is one 5 mg tablet daily with or without food (see CLINICAL TRIALS).

Dosage in Renal Insufficiency

No adjustment in dosage is required in patients with varying degrees of renal insufficiency (creatinine clearances as low as 0.15 mL/s [9 mL/min]) as pharmacokinetic studies did not indicate any change in the disposition of finasteride.

Dosage in Geriatrics
No adjustment in dosage is required although pharmacokinetic studies indicated the elimination of finasteride is decreased in patients more than 70 years of age (see DETAILED PHARMACOLOGY, Pharmacokinetics).

Missed Dose
If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Finasteride a synthetic 4-azasteroid compound, is an 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. Finasteride is highly effective in reducing circulating and intraprostatic DHT. Finasteride has very low affinity for the androgen receptor.

In the Finasteride Long-Term Efficacy and Safety Study, the effect of therapy with finasteride on BPH-related urologic events (surgical intervention [e.g., transurethral 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 finasteride 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.

Pharmacokinetics
In a study in 15 healthy male subjects, the mean bioavailability of a Accel-Finasteride Tablets USP 5 mg was 63% (range, 34-108%), based on the ratio of the area under the curve (AUC) relative to a 5 mg intravenous dose infused over 60 minutes. Maximum finasteride plasma concentration averaged 37 ng/mL (range, 27-49 ng/mL) and was reached 1 to 2 hours postdose. The mean plasma half-life of elimination was 6 hours (range, 3-16 hours). Following the intravenous infusion, mean plasma clearance was 2.75 mL/s (range, 1.17 - 4.65 mL/s) (165 mL/min, range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44-96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

Additional Pharmacokinetic/Pharmacodynamic data are provided under DETAILED PHARMACOLOGY, Human Pharmacology

Special Populations and Conditions

Geriatrics: No dosage adjustment is necessary for the elderly or patients with renal insufficiency.

STORAGE AND STABILITY

Store at room temperature (15°C - 30°C) and protect from light.

SPECIAL HANDLING INSTRUCTIONS

Women should not handle crushed or broken Accel-Finasteride Tablets USP when they are or may potentially be pregnant (see WARNINGS AND PRECAUTIONS, Special Populations, Exposure to Finasteride - Risk to Male Fetus).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each film-coated tablet for oral administration contains 5 mg of finasteride and the following non-medicinal ingredients: microcrystalline cellulose, hydroxyl propyl methyl cellulose, polyethylene glycol, coloring agents (FD&C blue 2 aluminum lake, titanium dioxide, iron oxide yellow), pregelatinized starch, lauroyl macrogoglycerides, lactose monohydrate, magnesium stearate and sodium starch glycolate.

Accel-Finasteride Tablets USP are blue colored, modified apple shaped, biconvex, film-coated tablets, debossed with ‘F’ on one side and ‘5’ on the other side. Available in blister packages of 30 tablets and bottle packages of 30, 100 and 500 tablets.

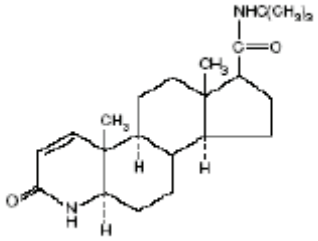
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	finasteride
Chemical name:	*N*-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide
Molecular formula:	$C_{23}H_{36}N_2O_2$
Molecular mass:	372.55 g/mol

Structural formula:



Physicochemical properties:

Description:	Finasteride is a white, crystalline solid with a melting point of approximately 257°C. It is freely soluble in chloroform and in lower alcohol solvents, but is practically insoluble in water (0.05 mg/mL at 25°C).

CLINICAL TRIALS

Comparative Bioavailability

Summary of studies establishing bioequivalence of Accel-Finasteride Tablets USP 5 mg to Proscar® 5 mg tablets (Reference Listed Drug)

Statistical summary of the comparative Bioavailability data:

A single dose 2-way cross-over bioequivalence study of Accel-Finasteride Tablets USP and Proscar® (finasteride) 5 mg tablets administered as 1 X 5 mg tablets in healthy adult male volunteers under fasting conditions (n=27) was conducted. The results indicate that Accel-Finasteride Tablets USP are bioequivalent to Proscar® 5 mg tablets. A summary of the results is presented in the following table:

Finasteride (5 mg Tablets) From measure data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV%)				
Parameter	**Accel-Finasteride Tablets USP (finasteride) Manufactured by Intas Pharmaceuticals Ltd., Matoda, India**	**PROSCAR® (finasteride) 5 mg tablet Manufactured by Merck Frosst Canada Ltd.**	**% Ratio of Geometric Means**	**Confidence Interval 90%**
AUC_T (ng•h/mL)	420.862, 438.972 (28.1%)	396.212, 416.453 (32.6%)	106.1%	100.29 – 112.34%
AUC_I (ng•h/mL)	437.621, 459.830 (30.8%)	413.462, 438.354 (35.3%)	105.8%	99.97 – 111.93%
C_{max} (ng/mL)	49.230, 50.583 (24.2%)	47.236, 48.525 (24.3%)	104.0%	98.64 – 109.61%
T_{max} [§] (h)	2.330 (1.250 – 4.000)	2.670 (1.250 – 4.000)		
$T_{1/2}$ [†] (h)	7.248 (32.5%)	7.369 (33.5%)		

[§] Expressed as the median (range) only
[†] Expressed as the arithmetic mean (CV%) only

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, suggests that finasteride reverses the progression of BPH in men with an enlarged prostate.

Finasteride 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 finasteride 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.

Finasteride was further evaluated in the Finasteride Long-Term Efficacy and Safety Study, a double-blind, randomized, placebo-controlled, 4-year multicenter study. In this study, the effect of therapy with finasteride 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 (see below for discussion of efficacy). Investigators collected adverse experience information reported by patients during each visit to the clinic and were asked to assess drug relationship. The drug-related adverse experiences seen in Finasteride Long-Term Efficacy and Safety Study were consistent with those seen in previous studies and are presented in the ADVERSE REACTIONS section. Although the clinical significance is unclear, a higher incidence of cataracts (4.2%, finasteride vs. 2.5%, placebo) and diabetes (2.8%, finasteride vs. 1.7%, placebo) was observed in patients receiving finasteride. None of these cases were considered drug related by the investigator.

Effect on Acute Urinary Retention and the Need for Surgery

In the 4-year Finasteride Long-Term Efficacy and Safety 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 finasteride, representing a 51% reduction in risk for surgery or acute urinary retention over 4 years. Finasteride reduced the risk of surgery by 55% (10.1% for placebo vs. 4.6% for finasteride) and reduced the risk of acute urinary retention by 57% (6.6% for placebo vs. 2.8% for finasteride). 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 2 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

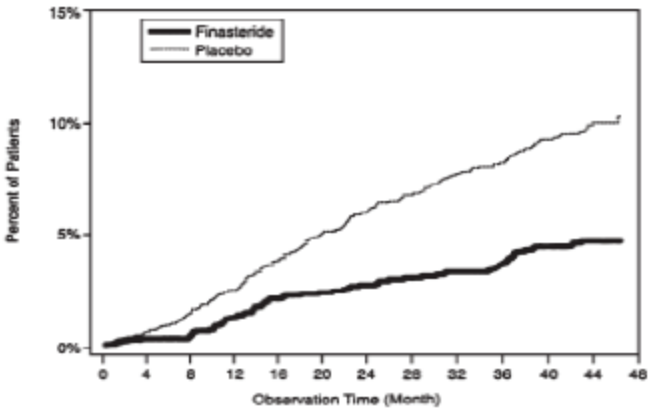


Figure 2
Percent of Patients Developing Acute Urinary Retention
(Spontaneous and Precipitated)

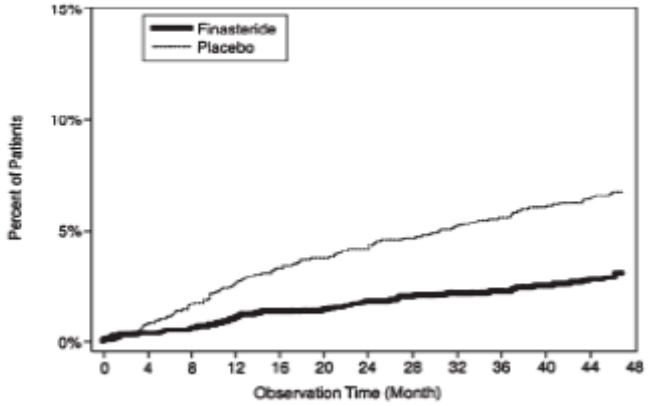


Table 2 Rates of Urologic Events and Risk Reduction by Finasteride over 4 Years

Urologic Events	Percentage 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 Finasteride Long-Term Efficacy and Safety 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, finasteride 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 finasteride, 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 Finasteride Long-Term Efficacy and Safety Study, there was a clear separation between treatment groups in maximum urinary flow rate in favor of finasteride 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, finasteride 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 Finasteride Long-Term Efficacy and Safety Study, prostate volume was assessed yearly by magnetic resonance imaging (MRI) in a subset of patients (n=284). In patients treated with finasteride, 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, finasteride 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 finasteride, 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.

Additional Clinical Trials
Urodynamic effects of finasteride in the treatment of bladder outlet obstruction due to BPH were assessed by invasive techniques in a 24-week, double-blind, placebo-controlled study of 36 patients with moderate to severe symptoms of urinary obstruction and a maximum flow rate of less than 15 mL/s. Relief of obstruction, as evidenced by significant improvement in detrusor pressure and increased mean flow rate, was demonstrated in patients treated with finasteride 5 mg compared to placebo.

The effect of finasteride on the volume of the peripheral and periurethral zones of the prostate in 20 men with BPH was evaluated by MRI in a one-year, double-blind, placebo-controlled study.

Patients treated with finasteride, but not those treated with placebo, experienced a significant decrease [11.5 ± 3.2 mL (SE)] in total gland size, largely accounted for by a reduction [6.2 ± 3 mL] in the size of

the periurethral zone. Since the periurethral zone is responsible for outflow obstruction, this reduction may account for the beneficial clinical response observed in these patients.

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 finasteride for BPH (see ADVERSE REACTIONS, Other Long Term Data).

DETAILED PHARMACOLOGY

Human 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 are 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, epididymis, 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 (t½ ~30 days). *In vitro* and *in vivo*, finasteride has been demonstrated to be a specific Type II 5α-reductase inhibitor, and has very low 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 four 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 four years. In these studies, circulating levels of testosterone were increased by approximately 10-20% yet remained within the physiologic range.

When finasteride 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 finasteride 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 pituitary-testicular axis was not affected. Treatment with finasteride 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, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; and 57% (range, 51-64%) was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.
There is a slow accumulation phase for finasteride after multiple dosing. After dosing with 5 mg/day of finasteride for 17 days, plasma concentrations of finasteride were 47% and 54% higher than after the first dose in men 45-60 years old (n=12) and ≥ 70 years old (n=12), respectively. Mean trough concentrations after 17 days of dosing were 6.2 ng/mL (range, 2.4-9.8 ng/mL) and 8.1 ng/mL (range, 1.8-19.7 ng/mL), respectively in the two age groups. Although steady state was not reached in this study, mean trough plasma concentration in another study in patients with BPH (mean age, 65 years) receiving 5 mg/day was 9.4 ng/mL (range, 7.1-13.3 ng/mL; n=22) after over a year of dosing.

The elimination rate of finasteride is decreased in the elderly, but no dosage adjustment is necessary. The mean terminal half-life of finasteride in subjects ≥ 70 years of age was approximately 8 hours (range, 6-15 hours) compared to 6 hours (range, 4-12 hours) in subjects 45-60 years of age. As a result, mean area

under the curve [AUC] (0-24 hr) after 17 days of dosing was 15% higher in subjects ≥ 70 years of age ($p = 0.02$).

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 0.15 to 0.92 mL/s (9.0 to 55 mL/min), AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}Cfinasteride were similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in BPH patients with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

In two studies of healthy subjects (n=69) receiving finasteride 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/mL) to 10.54 ng/mL. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving finasteride 5 mg/day ranged from undetectable (<1.0 ng/mL) to 21 ng/mL. Thus, based on a 5 mL ejaculate volume, the amount of finasteride in ejaculate was estimated 50- to 100-fold less than the dose of finasteride (5 micrograms) that had no effect on circulating DHT levels in adult males (see TOXICOLOGY, Developmental Studies).

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.

Animal Pharmacology

The ability of finasteride to inhibit 5α-reductase and block the formation of DHT in vivo was demonstrated using intact male rats and dogs. Studies were designed to demonstrate a decrease in prostatic levels of DHT or shrinkage in prostate size. Four hours after receiving a subcutaneous injection of 0.1 mg finasteride, rats showed a decrease in the concentration of DHT in the prostate. In dogs, treatment with finasteride 1 mg/kg given orally in four divided doses over an 18 hour period showed a reduction in the prostatic DHT concentration 6 hours after the final dose. These studies demonstrated that finasteride is active in vivo in blocking the formation of DHT.

The decreased levels of DHT also resulted in a decrease in prostate size. Prostate shrinkage was seen in intact mature dogs which received 1 mg/kg/day of finasteride by mouth for six weeks. A comparison of pre- and post-treatment prostate volumes showed that finasteride induced over 40% reduction in prostate size. A similar effect was noted in immature castrated male rats treated with testosterone. Finasteride, at oral doses of 0.1 mg/day, significantly inhibited the growth effect of exogenous testosterone on the accessory sex glands. This response is due to the specific inhibition of 5α-reductase as 2.5 mg/day of finasteride failed to block the ability of exogenous DHT to stimulate growth of the seminal vesicles and ventral prostate in treated animals.

Finasteride has no direct anti-androgen activity as shown by its lack of affinity for the androgen receptor in rat prostate cytosol. Concentrations of finasteride as high as 10^{-4}M did not prevent the binding of 3H-DHT whereas unlabelled DHT inhibited the binding with an IC_{50} of 2.9 nM.

Standard assays conducted in rats, mice and rabbits demonstrated that finasteride does not inhibit gonadotropin secretion or exhibit any antiestrogenic, uterotropic, antiprogestational, androgenic or progestational activity. These data are consistent with finasteride's acting as a specific 5α- reductase inhibitor with no other hormonal effects.

In a hepatotoxicity test, 40 mg/kg/day of finasteride was given orally to dogs for 28 days. Venous blood was analyzed for ALT (SGPT) and AST (SGOT). Neither transaminase was increased, illustrating that finasteride did not cause liver damage.

Ancillary pharmacology studies to assess effects on organ systems and biological parameters were conducted with finasteride. No important changes were seen in renal, gastric and respiratory functions in dogs, nor in the cardiovascular system of dogs and rats.

TOXICOLOGY

Acute Toxicity

Species	Sex	Finasteride Route	LD_{50} mg/kg
Mouse	Male	Oral	596
	Female	Oral	486
	Male	Intraperitoneal	391
	Female	Intraperitoneal	372
Rat	Male	Oral	967
	Female	Oral	418
	Male	Intraperitoneal	1027
	Female	Intraperitoneal	885
	Male	Subcutaneous	>2000
	Female	Subcutaneous	>2000
Dog	Male	Oral	>1000

Subacute and Chronic Toxicity Studies

The nature of the treatment-related changes in laboratory animals treated with finasteride are shown in Table 3.

Table 3 Finasteride - Target Organs Observed in Animal Studies

Treatment-Related Changes	Species	No Effect Dose (mg/kg/day)
Epididymal vacuolation (head)	Rat	0.1
Testes – Leydig cell hyperplasia	Rat	20
	Mouse	2.5
Leydig cell adenoma	Mouse	25
Liver – increased weight	Mouse	2.5
	Rat	5
	Dog	15
Thyroid – increased weight	Rat	5
Increased serum alkaline phosphatise	Dog	5

For most of the treatment-related changes seen in laboratory animals, a clear no-effect dose has been defined. Furthermore, most of the observed treatment-related effects can be categorized under three broad headings based on the current understanding of the drug-induced changes (Table 4).

Table 4 Treatment-Related Changes Seen in Laboratory Animals

Treatment-Related Changes	Species
Resulting from inhibition of 5α-reductase	
Decreased accessory sex glands weight	Rats, mice, dogs
Epididymis (head), vacuolation	Rats
Developmental effect s in male fetuses	Rats
Decreased fertility in males	Rats
Resulting from altered endocrine balance	
Leydig cell hyperplasia	Rats, mice
Leydig cell adenoma	Mice
Resulting from induction of drug metabolizing enzymes	
Increased liver weight	Mice, rats, dogs
Increased thyroid weight	Rats

Carcinogenesis and Mutagenesis

No evidence of a tumorigenic effect was observed in a 24-month study in rats receiving doses of finasteride of 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) (Table 4).

In mice, at a dose of 25 mg/kg/day, and in rats, at a dose of ≥ 40 mg/kg/day (250 and ≥ 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 (Table 3).

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) (Table 3).

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 μmol/L) 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. Furthermore, the concentrations (450-550 μmol/L) 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 rats treated with finasteride is due, at least in large part, to its effect on accessory sex organs (prostate and seminal vesicles) with failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in humans 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 μg/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 ≥ 30μg/kg/day (≥ 30% of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride in doses ≥ 3 μg/kg/day (≥ 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 5α-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 5α- 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 fetal 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 fetuses. In confirmation of the relevance of the rhesus model for human fetal 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 fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

REFERENCES

1. Andersen JT, Nickel JC, Marshall VR, Schulman CC, Boyle P. Finasteride significantly reduces acute urinary retention and the need for surgery in patients with symptomatic benign prostatic hyperplasia. Urology 1997;49(6):839-45.
2. Andersen JT, Ekman P, Wolf H, Beisland HO, Johansson JE, Kontturi M, Lehtonen T, Tveter K, The Scandinavian BPH study group. Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. Urology 1995;46(5):631-7.
3. Barry MJ. Epidemiology and natural history of benign prostatic hyperplasia. Urol Clin North Am 1990;17(3):495-507.
4. Barry M, Carlton CE, Coffey D, Fitzpatrick J, Griffiths K, Hald T, Holtgrewe L, Jardin A, McConnell J, Mebust W, Murphy G, Roehrborn C, Smith P, Steg A. World Health Organization Consensus Committee recommendations concerning: 1. Prostate symptom score (WHO-PSS) and quality of life assessment. 2. Diagnostic work-up of patients presenting with symptoms suggestive of prostatism. 3. Patient evaluation for research studies. Prog en Urol 1991;(1):957-72.
5. Gormley GJ, Stoner E, Bruskewitz RC, Imperato-McGinley J, Walsh PC, McConnell JD, Andriole GL, Geller J, Bracken BR, Tenover JS, Vaughan ED, Pappas F, Taylor A, Binkowitz B, Ng J, for the Finasteride Study Group. The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med 1992; 327:1185-91.
6. Gormley GJ, Stoner E, Rittmaster RS, Gregg H, Thompson DL, Lasseter KC, Vlasses PH, Stein EA. Effects of finasteride (MK-906), a 5α-reductase inhibitor, on circulating androgens in male volunteers. J Clin Endocrinol Metab 1990;70(4):1136-41.
7. Guess HA, Heyse JF, Gormley GJ. The effect of finasteride on prostate-specific antigen in men with benign prostatic hyperplasia. Prostate 1993;22(1):31-37.
8. Guess HA, Heyse JF, Gormley GJ, Stoner E, Oesterling JE. Effect of finasteride on serum PSA concentration in men with benign prostatic hyperplasia. Urol Clin N Am 1993; 20(4):627-36.
9. Nickel JC, Fradet Y, Boake RC, Pommerville PJ, Perreault J-P, Afridi SK, Elhilali MM, Prospect Study Group. Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). Can Med Assoc J 1996;155(9):1251-9.
10. Stoner E, Members of the Finasteride Study Group. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. Urology 1994; 43(3):284-94.
11. Tammela TLJ, Kontturi M J. Urodynamic effects of finasteride in the treatment of bladder outlet obstruction due to benign prostatic hyperplasia. J Urol 1993;149(2):342- 44.
12. Tempany CMC, Partin AW, Zerhouni EA, Zinreich SJ, Walsh PC. The influence of finasteride on the volume of the peripheral and periurethral zones of the prostate in men with benign prostatic hyperplasia. Prostate 1993;22 (1):39-42
13. Thompson IM, Goodman PJ, M.S., Tangen CM, Lucia MS, M.D., Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman,

CA Jr. The Influence of Finasteride on the Development of Prostate Cancer. N Engl J Med 2003;349:211-20.

14. Vermeulen A, Giagulli VA, De Schepper P, Buntinx A, Stoner E. Hormonal effects of an orally active 4-azasteroid inhibitor of 5α-reductase in humans. The Prostate 1989; 14(1):45-53.

15. PROSCAR® (finasteride, USP) Control no # 154826, Product Monograph. Merck Canada Inc. (May 8, 2012)

PART III: CONSUMER INFORMATION

[Pr]Accel-Finasteride Tablets USP
finasteride

This leaflet is part III of a three-part "Product Monograph" published when Accel-Finasteride Tablets USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Accel-Finasteride Tablets USP. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

ACCEL-FINASTERIDE TABLETS USP IS FOR USE BY MEN ONLY.

What the medication is used for:
Accel-Finasteride Tablets USP is used to treat symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Accel-Finasteride Tablets USP may also be used to reduce the risk of developing a sudden inability to pass urine and the need for surgery.

Accel-Finasteride Tablets USP is not approved for the prevention of prostate cancer.

What it does:
Accel-Finasteride Tablets USP lowers levels of a key hormone called DHT (dihydrotestosterone), which is a major cause of prostate growth. Lowering DHT leads to shrinkage of the enlarged prostate gland in most men. This can lead to gradual improvement in urine flow and symptoms over the next several months. Accel-Finasteride Tablets USP will help reduce the risk of developing a sudden inability to pass urine (acute urinary retention) and the need for surgery.

When it should not be used:
Do not take Accel-Finasteride Tablets USP if you think you are allergic to any of its ingredients.

Women and children should not take Accel-Finasteride Tablets USP. Women who are or may potentially be pregnant must not use Accel-Finasteride Tablets USP (see WARNINGS AND PRECAUTIONS, Pregnancy).

What the medicinal ingredient is:
finasteride

What the important nonmedicinal ingredients are:
microcrystalline cellulose, hydroxyl propyl methyl cellulose, polyethylene glycol, coloring agents (FD&C blue 2 aluminum lake, titanium dioxide, iron oxide yellow), pregelatinized starch, lauroyl macrogoglycerides, lactose monohydrate, magnesium stearate and sodium starch glycolate.

What dosage forms it comes in:
Each film coated tablet contains 5 mg of finasteride.

WARNINGS AND PRECAUTIONS

Pregnancy: Women who are or may potentially be pregnant must not use Accel-Finasteride Tablets USP. They should also not handle crushed or broken tablets of Accel-Finasteride Tablets USP. If the active ingredient in Accel-Finasteride Tablets USP is absorbed after oral use or through the skin by a woman who is pregnant with a male baby, it may cause the male baby to be born with abnormalities of the sex organs.

Accel-Finasteride Tablets USP are coated and will prevent contact with the active ingredient during normal handling provided that the tablets are not broken or crushed. If a woman who is pregnant comes into contact with the active ingredient in Accel-Finasteride Tablets USP, a physician should be consulted.

You must see your physician regularly while taking Accel-Finasteride Tablets USP. Follow your physician's advice about when to have these checkups.

About Prostate Specific Antigen (PSA). Your physician may have done a blood test called PSA for the screening of prostate cancer. Accel-Finasteride Tablets USP can alter PSA values. You should tell your physician that you are taking Accel-Finasteride Tablets USP. For more information, talk to your physician.

Accel-Finasteride Tablets USP may increase the chance of a more serious form of prostate cancer.

INTERACTIONS WITH THIS MEDICATION

Tell your physician or pharmacist about all the medicines you take. This includes prescription and non-prescription medicines, and herbal supplements.

PROPER USE OF THIS MEDICATION

Take Accel-Finasteride Tablets USP as your physician has prescribed.

Usual dose:
5 mg tablet once daily by mouth with or without food

Missed dose:
If you miss a dose, do not take an extra one. Just take the next tablet as usual.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medicine, Accel-Finasteride Tablets USP may cause side effects. Side effects due to Accel-Finasteride Tablets USP may include:

- impotence (an inability to have an erection)
- less desire to have sex.
- problems with ejaculation, such as a decrease in the amount of semen released during sex.

In addition, some men may have breast swelling and/or tenderness. Some men have also reported the following:

- allergic reactions such as rash, itching, hives and swelling of the lips and face
- testicular pain.
- an inability to have an erection that continued after stopping the medication
- male infertility and/or poor quality of semen.
- Improvement in the quality of semen has been reported after stopping the medication.
- depression
- decrease in sex drive that continued after stopping the medication.

In rare cases, male breast cancer has been reported.

You should promptly report to your physician any changes in your breasts such as lumps, pain or nipple discharge.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / Effects		Talk with your physician or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Allergic reactions including rash, hives, and swelling of the lips and face			√

This is not a complete list of side effects. For any unexpected effects while taking Accel-Finasteride Tablets USP, contact your physician or pharmacist.

HOW TO STORE IT

Store at room temperature (15°C – 30°C) and protect from light.

KEEP ACCEL-FINASTERIDE TABLETS USP AND ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Report Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor at the following address:

Accel Pharma Inc.
99 Place Frontenac
Pointe-Claire, QC, H9R 4Z7
Canada

Manufactured by:
Intas Pharmaceuticals Limited,
Plot No.: 457, 458,
Village – Matoda
Bavla Road, TA. – Sanand
Dis. – Ahmedabad-382 210
INDIA

This leaflet is prepared by Accel Pharma Inc.

Last revised: January 28, 2013