PRODUCT INFORMATION

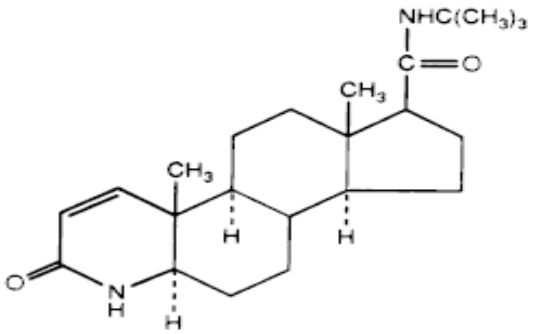
APO-Finasteride 5
(Finasteride Film-coated Tablets 5 mg)

NAME OF THE MEDICINE

Finasteride is described chemically as: N-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.

The CAS No is 98319-26-7.

The empirical formula is $C_{23}H_{36}N_2O_2$ and the molecular weight is 372.55. The structural formula is:



DESCRIPTION

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

Composition

Active: Finasteride

Inactives: Lactose, microcrystalline cellulose, pregelatinised maize starch, lauroyl macrogolglycerides, sodium starch glycollate, magnesium stearate and Opadry 03F20404 Blue.

PHARMACOLOGY

Mechanism of Action

Finasteride is a synthetic 4-azasteroid compound, is a specific inhibitor of Type II 5α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Finasteride is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

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 conversion of testosterone to the potent androgen, dihydrotestosterone (DHT) within the prostate. 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. *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 vary over 24 hours, serum DHT levels remain constant during this period indicating that plasma concentrations of medicine 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, serum prostate-specific antigen (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 finasteride was given for 7-10 days to patients scheduled for prostatectomy, the medicine caused an approximate 80% decrease in intraprostatic DHT. 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, oestradiol, 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 0.6mL 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 C19 and C21 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

Absorption

Maximum finasteride plasma concentrations are reached approximately two hours after dosing and absorption is complete after six to eight hours. Oral bioavailability of finasteride is approximately 80%. Bioavailability is not affected by food.

Distribution

Protein binding is approximately 93%. Volume of distribution of finasteride is approximately 76L. A multiple-dose study demonstrated a slow accumulation of small amounts of finasteride over time. After daily dosing of 5 mg /day, trough plasma concentrations of finasteride of about 8-10 ng/mL were reached and these remained stable over time.

Finasteride has been recovered in the cerebrospinal fluid (CSF) of patients treated with a 7-10 day course of finasteride, but the medicine does not appear to concentrate preferentially in the CSF. Finasteride has also been recovered in the seminal fluid of subjects receiving 5mg of finasteride daily (see Warnings and Precautions). The amount of finasteride in the seminal fluid is 50- to 100-fold less than the dose of finasteride (5µg) that had no effect on circulating DHT levels in adult males (see also DEVELOPMENTAL STUDIES).

Metabolism

Finasteride is metabolised primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of ^{14}C-finasteride in man two metabolites of finasteride were identified which possess not more than 20% of the Type II 5α-reductase inhibiting activity of finasteride.

Elimination

Finasteride displays a mean plasma elimination half-life of six hours. Plasma clearance of finasteride is approximately 165 mL/min. Following an oral dose of ^{14}C-finasteride, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged medicine was excreted in the urine) and 57% of total dose was excreted in the faeces.

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 over 70 years of age. This finding appears to be of no clinical significance and hence a reduction in dosage is not warranted.

In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, area under the curve (AUC), maximum plasma concentrations, half-life, and protein binding of unchanged finasteride after a single dose of ^{14}C-finasteride 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 faecal 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. Therefore it is not necessary to adjust dosage in patients with renal insufficiency that is not dialysed, as the therapeutic window of finasteride is adequate and as a correlation between creatinine clearance and accumulation could not be demonstrated.

Race

The effect of race on finasteride pharmacokinetics has not been studied.

Hepatic Insufficiency

The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied.

Bioequivalence Study

An open label, balanced, randomized, two-treatment, two period, two-sequence, single dose, two-way crossover, comparative oral bioavailability study of two formulations of Finasteride Film-coated Tablets 5 mg was conducted in 30 healthy adult human male subjects under fasting conditions. The study compared Finasteride Film-coated Tablets 5 mg with reference product Proscar® 5mg tablets.

Statistical comparisons of geometric means for Test vs. Reference for finasteride C_{max} and $AUC_{0-\infty}$ were as follows:

Parameters (units)	**Geometric Least Squares Mean**			**90% Confidence Interval (Parametric)**
	Test Product B	Reference Product A	Ratio B/A%	
C_{max} (ng/mL)	52.717	47.293	111.5	106.28-116.91%
$AUC_{0-\infty}$ (ng.h/mL)	427.803	395.307	108.2	101.48-115.41%

This comparison of test product with reference product finasteride met the predefined criteria for bioequivalence, as the calculated 90% CI for all ratios of pre-specified In-Transformed PK parameters fell within the range 80.00%-125.00%.

CLINICAL TRIALS

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 5mg/day was initially evaluated in patients with symptoms of BPH and enlarged prostates by digital rectal examination in two 1-year, placebo-controlled, randomised, double-blind, Phase III studies and their 5-year open extensions. Of 536 patients originally randomised to receive finasteride 5mg/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 (PLESS), a double-blind, randomised, placebo-controlled, 4-year, multicentre study. In this study, the effect of therapy with finasteride 5mg/day on symptoms of BPH and BPH-related urologic events (surgical intervention [eg. transurethral resection of the prostate (TURP) and prostatectomy] or acute urinary retention requiring catheterisation) was assessed. 3040 patients between the ages of 45 and 78, with moderate to severe symptoms of BPH and an enlarged prostate upon digital examination, were randomised 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.

Investigators collected adverse experience information reported by patients during each visit to the clinic and were asked to assess medicine-relationship. The medicine-related adverse experiences seen in PLESS were consistent with those seen in previous studies and are presented in the Adverse Effects section. Although the clinical significance is unclear, a higher incidence of cataracts (4.2% finasteride vs. 2.5% placebo) was observed in patients receiving finasteride. None of these cases were considered medicine-related by the investigator.

Effect on Acute Urinary Retention and the Need for Surgery

In the 4-year PLESS study, surgery or acute urinary retention requiring catheterisation 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. Table 1 below shows the rates of occurrence and risk reduction of urologic events during the study.

Table 1
RATES OF UROLOGIC EVENTS AND RISK REDUCTION BY FINASTERIDE 5 mg OVER 4 YEARS

	Percent (Number) of Patients		
Urologic Events	**Placebo (n= 1503) % n**	**Finasteride (n=1513) % n**	**Risk Reduction**
Surgery or Acute Urinary Retention	13.2 (n=199)	6.6 (n=100)	51 %*
Surgery † TURP	10.1 (n=152) 8.3 (n=125)	4.6 (n=69) 4.2 (n=64)	55 %* 49 %*
Acute Urinary Retention	6.6 (n=99)	2.8 (n=42)	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 symptoms 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, 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, a Phase III study, 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 favour of finasteride by month 4, which was maintained throughout the study. Mean maximum urinary flow rate at baseline was approximately 11mL/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 1.9mL/sec compared with 0.2mL/sec in the placebo group.

Effect on Prostate Volume
In the two 1-year, Phase III studies mean prostate volume at baseline ranged between 40-50cc. 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 finasteride, prostate volume was reduced compared with both baseline and placebo throughout the 4year 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 55.9cc at baseline to 45.8cc at 4 years) compared with an increase of 14.1% (from 51.3cc to 58.5cc) 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 (approx. 40cc and greater) at baseline.

INDICATIONS

Apo-Finasteride 5 is indicated for the treatment of patients with symptomatic benign prostatic hyperplasia (BPH) with an enlarged prostate.

CONTRAINDICATIONS

Apo-Finasteride 5 is contraindicated in the following:

- Use in women when they are or may potentially be pregnant (See WARNINGS AND PRECAUTIONS: USE IN PREGNANCY: EXPOSURE TO FINASTERIDE - RISK TO A MALE FOETUS; and PRESENTATION: STORAGE AND HANDLING)
- Hypersensitivity to any component of this product

Apo-Finasteride 5 is not indicated for use in women or children.

PRECAUTIONS

General

Since the beneficial response to Apo-Finasteride 5 may not be manifested immediately, patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.

Apo-Finasteride 5 may not reduce inconvenience to patients arising from benign prostatic hyperplasia symptoms in patients with mild to moderate enlargement in prostate (< 40 mL size).

Effects on PSA and Prostate Cancer Detection

No clinical benefit has yet been demonstrated in patients with prostate cancer treated with finasteride. Patients with BPH and elevated PSA were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these BPH studies, finasteride did not appear to alter the rate of prostate cancer detection and the overall incidence of prostate cancer were not significantly different in patients treated with finasteride or placebo.

Digital rectal examinations, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with finasteride and periodically thereafter. Serum PSA is also being used as one of the components of the screening process to detect prostate cancer.

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

finasteride. A baseline PSA< 4 ng/mL does not exclude prostate cancer.

Finasteride causes a decrease in serum PSA levels by approximately 50% in patients with BPH, even in the presence of prostate cancer. This decrease in serum PSA levels should be considered when evaluating PSA laboratory 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 finasteride Long-Term Efficacy and Safety Study (PLESS) confirmed that in typical patients treated with finasteride 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 INCREASES IN PSA LEVELS WHILE ON FINASTERIDE SHOULD BE CAREFULLY EVALUATED, INCLUDING CONSIDERATION OF NON-COMPLIANCE TO THERAPY WITH FINASTERIDE.

Use in Pregnancy (Category X)

Medicines which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Apo-Finasteride 5 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 medicines, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

Exposure to Finasteride - Risk to A Male Foetus

Crushed or broken tablets of Apo-Finasteride 5 should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see USE IN PREGNANCY). Apo-Finasteride 5 tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Small amounts of finasteride have been recovered in the seminal fluid of subjects receiving 5 mg of Finasteride daily. The maximum levels detected in 2 different studies were 10.54 and 21 ng/mL which are 50- to 100-fold less than the dose of finasteride (5µg) that had no effect on circulating DHT levels in adult males (see also DEVELOPMENTAL STUDIES).

Developmental Studies

Dose-dependent 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 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 ≥ 30 µg/kg/day (≥30% of the recommended human dose and decreased anogenital distance when given finasteride in doses ≥ 3 µg/kg/day (≥3% of the recommended human dose). 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). No developmental abnormalities have been observed in first generation male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day), with untreated females.

No evidence of malformations has been observed in rabbit foetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day.

Treatment of male rabbits with finasteride up to 80 mg/kg/day (543 times human exposure) did not impair fertility. In male rats, treatment for up to 24 or 30 weeks with 80 mg/kg/day (61 times human exposure) resulted in an apparent decrease in fertility associated with a significant decrease in weight of seminal vesicles and prostate. All of these effects were reversible within 6 weeks of discontinuation of treatment. This decrease in fertility in rats was secondary to the effect of finasteride on the accessory sex organs, resulting in failure to form a seminal plug, which is essential for fertility in rats, but is not relevant to man.

The *in utero* effects of finasteride exposure during the period of embryonic and foetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 60 to 120 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5mg/day) resulted in no external genital abnormalities in male foetuses. In confirmation of the relevance of the rhesus model for human foetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 20 times the recommended human dose or approximately 1-2 million times the highest estimated exposure to finasteride from semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride related abnormalities were observed in female foetuses at any dose.

Use in Lactation

Apo-Finasteride 5 is not indicated for use in women.
It is not known whether finasteride is excreted in human milk.

Paediatric Use

Apo-Finasteride 5 is not indicated for use in children.
Safety and effectiveness in children have not been established.

Carcinogenesis and Mutagenesis

In a 24 month carcinogenicity study in rats there was an increase in the incidence of thyroid follicular adenomas in male rats receiving 160 mg/kg/day finasteride (statistically significant trend test). This dose produced a systemic exposure in rats 111 times that observed in humans at the recommended dose (based on AUC ($_{0\text{-}24\ hrs}$) values). The effect of finasteride on the thyroid in rats appears to be due to an increased rate of thyroxine clearance and not a direct effect on the medicine. These observations seen in the rat are thought not relevant to man.

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; no adenomas were seen in mice given 2.5 or 25 mg /kg/day.

In mice at a dose of 25 mg /kg/day and in rats at a dose of ≥40 mg/kg/day, an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cell and the increase in serum luteinizing hormone (LH) levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. This suggests the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

No medicine-related Leydig cell changes were seen in rats or dogs treated with finasteride for one year at doses of 20 mg/kg/day and 45 mg /kg/day respectively, or in mice treated for 19 months at a dose of 2.5 mg /kg/day.

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 µmol) 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 5mg. Further, the concentrations

(450-550 µmol) 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).

INTERACTIONS WITH OTHER MEDICINES

No medicine interactions of clinical importance have been identified. Compounds which have been tested in man have included propranolol, digoxin, glibenclamide, theophylline, warfarin and phenazone. Increases in P-450 medicine-metabolising activity were observed in animal studies (in rats, mice and dogs) receiving doses of >80, 250 and 45 mg /kg/day respectively. Finasteride is metabolised primarily via the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other medicines is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4 will affect the plasma concentration of finasteride. However, based on established safety margins, any increase due to concomitant use of such inhibitors is unlikely to be of clinical significance.

In a study in 12 normal volunteers receiving finasteride 5mg/day for 8 days, finasteride significantly increased theophylline clearance by 7% and decreased its half life by 10% after intravenous administration of aminophylline. These changes are not clinically significant.

Other Concomitant Therapy

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

Effects on Laboratory Tests

When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels decrease in patients treated with finasteride. In most patients, a rapid decrease in PSA is seen within the first months, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with 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.

ADVERSE EFFECTS

Finasteride is well tolerated.

4-Year Placebo-Controlled Study
In PLESS, 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 adverse 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 adverse effects related to sexual function, which were the most frequently reported adverse effects.

Table 2 presents the only clinical adverse effects considered possibly, probably or definitely medicine-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 or ejaculation disorder.

TABLE 2

Drug-Related Adverse Experiences

	Treatment	Year 1 % (n)	Years 2, 3 and 4* % (n)
Impotence	Placebo	3.7 (n=56)	5.1 (n=77)
	Finasteride	8.1 (n=123)	5.1 (n=77)
Decreased Libido	Placebo	3.4 (n=52)	2.6 (n=39)
	Finasteride	6.4 (n=98)	2.6 (n=39)
Decreased Volume of Ejaculate	Placebo	0.8 (n=12)	0.5 (n=7)
	Finasteride	3.7 (n=56)	1.5 (n=23)
Ejaculation Disorder	Placebo	0.1 (n=1)	0.1 (n=1)
	Finasteride	0.8 (n=12)	0.2 (n=3)
Breast Enlargement	Placebo	0.1 (n=1)	1.1 (n=17)
	Finasteride	0.5 (n=8)	1.8 (n=27)
Breast Tenderness	Placebo	0.1 (n=1)	0.3 (n=5)
	Finasteride	0.4 (n=6)	0.7 (n=11)
Rash	Placebo	0.2 (n=3)	0.1 (n=2)
	Finasteride	0.5 (n=8)	0.5 (n=7)

* Combined years 2-4
N= 1524 and 1516, finasteride vs placebo, respectively.

Phase III Studies and 5-Year Extensions.
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 finasteride. The incidence of new medicine-related sexual adverse experiences decreased with duration of treatment with finasteride.

Post-Marketing Experience

The following adverse experiences have been reported in post-marketing use. Because these reactions are reported voluntarily from a population of an 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 rash, pruritus, urticaria and swelling of the lips, tongue, throat and face.

Psychiatric disorders: depression; 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; breast tenderness and enlargement; male breast cancer; testicular pain; male infertility and/or poor seminal quality. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.

Other Long-Term Data

Prostate Cancer Trial
A 7-year, placebo-controlled trial, sponsored by the US National Cancer Institute, has shown that subjects in the finasteride group had proportionately more high-grade prostate cancers (Gleason scores 7, 8, 9 & 10) detected on needle biopsy compared to subjects in the placebo group (6.4% vs. 5.1% of evaluated patients). The clinical significance of these findings is currently unknown.

Breast Cancer in Men
Eleven cases of breast cancer in men have been reported in clinical trials of finasteride. Eight of these were in long-term trials including 2 cases in PLESS (4 years duration; both in the placebo group), 4 cases in MTOPS (>4 years duration, all in a finasteride group) and 2 cases in PCPT (7 years duration, one each in the finasteride and placebo groups). The clinical significance of these findings is currently

unknown.

DOSAGE AND ADMINISTRATION

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

Dosage in Renal Insufficiency

Adjustments in dosage are not necessary 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.

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. No specific treatment of overdosage with finasteride is recommended. General supportive care should be given.

The Poisons Information Centre, telephone number 13 11 26 should be contacted for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Apo-Finasteride 5 (AUST R 155238)

Apo-Finasteride 5 comes as a blue, round, biconvex, film-coated tablets, marked ‘F5’ on one side and plain on the other and are available in a pack containing 30 tablets in foil blisters.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sponsor:
Pharmacor Pty Ltd
Suite 501, 7 Oaks Ave
Dee Why NSW 2099
Australia

Distributor in Australia:
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

26 March 2010

DATE OF MOST RECENT AMENDMENT

27 January 2016