AUSTRALIAN PRODUCT INFORMATION – FINNACAR (FINASTERIDE) TABLETS

1 NAME OF THE MEDICINE

Finasteride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FINNACAR tablets contain 5 mg of finasteride.

Excipients with known effect: Lactose monohydrate

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

FINNACAR White, rounded triangle tablet marked with R/G on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of patients with symptomatic benign prostatic hyperplasia (BPH) with an enlarged prostate.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Impaired renal function

Adjustments in dosage are not necessary in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 mL/minute) as pharmacokinetic studies did not indicate any change in the disposition of finasteride.

Use in the elderly

No adjustment in dosage is required although pharmacokinetic studies indicated that the elimination of finasteride is somewhat decreased in patients aged over 70 years.

Handling

Crushed or broken tablets of FINNACAR should not be handled by women when they are or may potentially be pregnant (see section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy, Risk to a male fetus of exposure to finasteride).

4.3 CONTRAINDICATIONS

Use in women when they are or may potentially be pregnant (see section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy, Risk to a male fetus of exposure to finasteride and section 4.2 DOSE AND METHOD OF ADMINISTRATION Handling).

Hypersensitivity to any component of this product.

Use in women or children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

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

Effects on prostate specific antigen (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 was 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 3,000 patients in the four 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 NONCOMPLIANCE WITH FINASTERIDE THERAPY.

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 section 4.8 ADVERSE EFFECTS]. Similar results were observed in a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride). 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.

Use in the elderly

No data available

Paediatric use

FINNACAR is not indicated for use in children. Safety and effectiveness in children have not been established.

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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE , Effects on prostate specific antigen and prostate cancer detection.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interactions of clinical importance have been identified. Compounds which have been tested in humans have included propranolol, digoxin, glibenclamide, warfarin and phenazone.

Increases in cytochrome P450 drug 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 drugs 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 5 mg/day for eight 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 angiotensin converting enzyme (ACE) inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H_2-antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Developmental studies

Dose dependent hypospadias were 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 greater than or equal to 30 μg/kg/day (greater than or equal to 30% of the recommended human dose), and decreased anogenital distance when given finasteride in doses greater than or equal to 3 μg/kg/day (greater than or equal to 3% of the recommended human dose). The critical period during which these effects can be induced has been defined in rats as days 16 to 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 the mating of finasteride treated male rats (80 mg/kg/day) with untreated females.

No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6 to 18 of gestation at doses of 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 six 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 humans.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20 to 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 to finasteride from semen of men taking 5 mg/day) resulted in no external genital 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 or approximately 1 to 2 million times the highest estimated exposure to finasteride from semen) 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.

Use in pregnancy – Pregnancy Category X (Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.)

FINNACAR is contraindicated for use in women when they are or may potentially be pregnant (see section 4.2 CONTRAINDICATIONS).

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

Risk to a male fetus of exposure to finasteride

Crushed or broken FINNACAR tablets 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 fetus (see **Use in pregnancy**). FINNACAR tablets are coated and will prevent contact with 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 finasteride 5 mg daily. The maximum levels detected in two different studies were 10.54 and 21 ng/mL which are 50- to 100-fold less than the dose of finasteride (5 μg) that had no effect on circulating DHT levels in adult males (see also Developmental studies).

Use in lactation.

FINNACAR is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Finasteride is well tolerated.

The most frequent adverse reactions are impotence and decreased libido. These adverse reactions occur early in the course of therapy and resolve with continued treatment in the majority of patients.

Four year placebo controlled study

In PLESS, 1,524 patients treated with finasteride 5 mg daily and 1,516 patients treated with placebo were evaluated for safety over a period of four years. 4.9% (74 patients) were discontinued from treatment due to adverse reactions 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 reactions related to sexual function, which were the most frequently reported adverse reactions.

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 greater than or equal to 1% and greater than placebo over the four years of the study. In years 2 to 4 of the study, there was no significant difference between treatment groups in the incidence of impotence, decreased libido or ejaculation disorder.

TABLE 1: DRUG RELATED ADVERSE EXPERIENCES

Adverse experience	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)

* Combines years 2-4

N = 1524 and 1516, finasteride vs placebo, respectively

Phase III studies and five year extensions

The adverse experience profile in the one year, placebo controlled, phase III studies and the five year extensions, including 853 patients treated for five to six years, was similar to that reported in years 2 to 4 in PLESS. There is no evidence of increased adverse experiences with increased duration of finasteride. The incidence of new drug related sexual adverse experiences decreased with duration of treatment with finasteride.

POSTMARKETING EXPERIENCE

The following additional adverse effects have been reported in post-marketing experience with PROSCAR and/or finasteride at lower doses. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure **Immune system disorders:**

Unknown: hypersensitivity reactions, including pruritis, urticaria, and angioedema (including swelling of the lips,, face, tongue and throat).

Psychiatric disorders:

Common: decreased libido

Unknown: decreased libido that may continue after discontinuation of therapy, depression, suicidal ideation

Cardiac disorders:

Unknown: palpitation

Hepatobiliary disorders:

Unknown: hepatic enzymes increased

Skin & subcutaneous tissue disorders:

Unknown: rash, pruritus, urticarial

Reproductive system & breast disorders:

Common: sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment

Uncommon: ejaculation disorder, breast tenderness, breast enlargement

Unknown: testicular pain, erectile dysfunction which may continue after discontinuation of treatment, male breast cancer, male infertility and/or poor seminal quality. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.

Investigations*:*

Common: decreased volume of ejaculate

OTHER LONG-TERM DATA

Prostate Cancer Trial:

The PCPT trial was a 7-year randomised, 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]. In a 4-year placebo-controlled clinical trial with another 5α-reductase inhibitor (dutasteride), similar results for Gleason score 8-10 prostate cancer were observed.

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

Breast Cancer in Men:

During the 4-to-6-year placebo and comparator-controlled Medical Therapy of Prostate Symptoms (MTOPS) study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-controlled men but no cases in men treated with finasteride. During the 7-year placebo-controlled PCPT that enrolled 18,882 men, there was 1 case of breast cancer in men treated with finasteride, and 1 case of breast cancer in men treated with placebo. There have been post-marketing reports of male breast cancer with the use of finasteride 1 mg and 5 mg. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Finasteride, 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.

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 threefold increase in the risk of acute urinary retention and prostate surgery. Men with enlarged prostates are also three 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 dose of finasteride 5 mg produced a rapid reduction in the serum concentration of DHT, with the maximum effect observed after eight hours. While plasma levels of finasteride vary over 24 hours, serum DHT levels remain 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, 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 four years. In these studies, circulating levels of testosterone were increased by approximately 10 to 20% yet remained within the physiological range.

When finasteride was given for seven to ten days to patients scheduled for prostatectomy, the drug caused an approximate 80% decrease in intraprostatic DHT. Intraprostatic concentrations of testosterone were increased up to ten times over pretreatment 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 two 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 luteinising hormone (LH) and 9% in follicle stimulating hormone (FSH) was observed in patients treated for 12 months, however, these levels remained well within the physiological range. Gonadotropin releasing hormone (GnRH) stimulated levels of LH and FSH were not altered, indicating that regulatory control of the pituitary-testicular axis was not affected. Treatment with 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 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 5α-reductase deficiency.

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, suggest the 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 one year, placebo controlled, randomised, double blind, phase III studies and their five year open extensions. Of 536 patients originally randomised to receive finasteride 5 mg/day, 234 completed an additional five 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 a Long-term Efficacy and Safety Study (PLESS), a double blind, randomised, placebo controlled, four year, multicentre study. In this study, the effect of therapy with finasteride 5 mg/day on symptoms of BPH and BPH related urological events (surgical intervention (e.g. 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 enlarged prostate upon digital examination, were randomised into the study, (1,524 to finasteride, 1,516 to placebo) and 3,016 patients were

evaluable for efficacy. 1,883 patients completed the four year study (1,000 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 drug relationship. The drug related adverse experiences seen in PLESS were consistent with those seen in previous studies and are presented in the **Adverse Effects (** section4.8). Although the clinical significance is unclear, a higher incidence of cataracts (4.2% finasteride versus 2.5% 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 four 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 four years. Finasteride reduced the risk of surgery by 55% (10.1% for placebo versus 4.6% for finasteride) and reduced the risk of acute urinary retention by 57% (6.6% for placebo versus 2.8% for finasteride). The reduction in risk was evident between treatment groups at first evaluation (four months) and was maintained throughout the four year study. Table 2 shows the rates of occurrence and risk reduction of urological events during the study.

Table 2: Rates of urological events and risk reduction by finasteride 5 mg over 4years

Urological 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[#]	10.1 (n = 152)	4.6 (n = 69)	55%*
TURP	8.3 (n = 125)	4.2 (n = 64)	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 one 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 six 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 five years of extension studies.

Patients in the four year PLESS study had moderate to severe symptoms at baseline (mean of approximately 15 points on a 0 to 34 point scale). In patients who remained on therapy for the duration of the four 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

one 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 one 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 five years of extension studies.

In the four 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 11 mL/second 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/second compared with 0.2 mL/second in the placebo group.

Effect on prostate volume

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

In the four 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 four 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 four 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 one year data from seven double blind, placebo controlled studies of a similar design, including 4,491 patients with symptomatic BPH, demonstrated that, in patients treated with finasteride, the magnitude of symptoms 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum finasteride plasma concentrations are reached approximately 1.5 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 76 L. 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 to 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 seven to ten day course of finasteride, but the drug does not appear to concentrate preferentially in the CSF. Finasteride has also been recovered in the seminal fluid of subjects receiving finasteride 5 mg daily (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The amount of finasteride in the seminal fluid is 50- to 100-fold less than the dose of finasteride (5 μg) that had no effect on circulating DHT levels in adult males (see also section 4.6 FERTILITY, PREGNANCY AND LACTATION- Developmental studies).

Metabolism

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

Excretion

Finasteride displays a mean plasma elimination half-life of 6 hours. Plasma clearance of finasteride is approximately 165 mL/minute. 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 drug 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 six hours in men aged 18 to 60 years to eight hours in men aged 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 to 55 mL/minute, 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 who are 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 impairment

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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 to 550 μmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 4,000 to 5,000 times the peak plasma levels in humans given a total dose of 5 mg. Further, the concentrations (450 to 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).

Carcinogenicity

In a 24 month carcinogenicity study in rats there was an increase in the incidence of thyroid follicular adenomas in male rats receiving finasteride 160 mg/kg/day (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 to 24 hours) 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 of the drug. These observations seen in the rat are thought not relevant to humans.

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 ≥ 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 luteinising hormone (LH) levels (two- to threefold above control) has been demonstrated in both rodent species treated with high doses of finasteride. This suggests the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following excipients: lactose monohydrate, microcrystalline cellulose, pregelatinised maize starch, sodium starch glycollate, purified talc, magnesium stearate, hyprolose, hypromellose, macrogol 6000 and titanium dioxide. The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister (PVC/Al) packs of 30

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

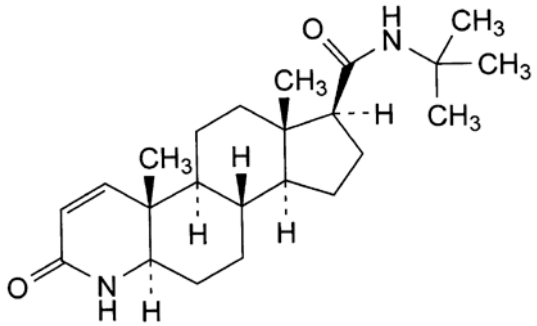
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Finasteride is a white or almost white, crystalline powder. It is practically insoluble in water, freely soluble in ethanol and in methylene chloride.

Chemical structure

Finasteride. The chemical name for finasteride is *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide. Its structural formula is:



$C_{23}H_{36}N_2O_2$ Molecular weight: 372.5

CAS number

98319-26-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Arrow Pharma Pty Ltd
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Cremorne VIC 3121
Australia
www.arrowpharma.com.au

9 DATE OF FIRST APPROVAL

17 December 2008

10 DATE OF REVISION

1 March 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	SRR change in line with innovator-add risk of high grade prostate cancer
4.8	SRR changes in line with innovator- post market experience-reformat in line with innovator and add adverse effects, long term data