SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Finasteride Aurobindo 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg finasteride.

Excipient with known effect: contains 97.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Blue coloured, circular (diameter is 7.6 mm), biconvex, beveled edged film-coated tablets debossed with 'E' on one side and '61' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Finasteride Aurobindo 5 mg is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in adult patients with enlarged prostate to:

- cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH,
- reduce the incidence of acute urinary retention and reduce need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

4.2 Posology and method of administration

Posology

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

Even though improvement can be seen within a short time, treatment for at least 6 months may be necessary in order to determine objectively whether a satisfactory response to treatment has been achieved.

Special population:

Dosage in the elderly
Dosage adjustments are not necessary although pharmacokinetic studies have shown that the elimination rate of finasteride is slightly decreased in patients over the age of 70.

Dosage in hepatic insufficiency
There is no data available in patients with hepatic insufficiency (see section 4.4).

Dosage in renal insufficiency
Dosage adjustments are not necessary in patients with varying degrees of renal insufficiency (starting from creatinine clearance as low as 9 ml/min) as in pharmacokinetic studies renal insufficiency was not found to affect the elimination of finasteride. Finasteride has not been studied in patients on haemodialysis.

Paediatric population
The safety and efficacy of Finasteride in children have not yet been established.
Finasteride Aurobindo is contraindicated in children.

Method of administration
For oral use only.
The tablet should be swallowed whole and must not be divided or crushed (See section 6.6).
Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1).

4.3 Contraindications

Finasteride Aurobindo is not indicated for use in women or children.

Finasteride Aurobindo is contraindicated in the following:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy – Use in women when they are or may potentially be pregnant (see 4.6 Pregnancy and lactation, Exposure to finasteride – risk to male fetus).

4.4 Special warnings and precautions for use

General:

- Consultation of an urologist should be considered in patients treated with finasteride.
- Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with finasteride.
- To avoid obstructive complications it is important that patients with large residual urine and/or heavily decreased urinary flow are carefully controlled. The possibility of surgery should be an option.

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 serum prostate specific antigen (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 statistically different in patients treated with finasteride or placebo.

Digital rectal examinations as well as other evaluations for prostate cancer are recommended prior to initiating therapy with finasteride and periodically thereafter. Serum PSA is also used for prostate cancer detection. Generally a baseline PSA > 10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal refrence 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 concentrations by approximately 50% in patients with BPH, even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with finasteride should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Analysis of PSA data from over 3000 patients in the 4-year, double-blind, placebo-controlled 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 increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to finasteride therapy.

Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride. The ratio of free to total PSA remains constant even under the influence of finasteride. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment to its value is necessary.

Drug/laboratory test interactions

Effect on levels of PSA
Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels decrease in patients treated with finasteride. 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 4.4 Special Warnings and precautions for use, Effects on PSA and prostate cancer detection.

Breast cancer in men
Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and in the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Pediatric population:
Finasteride Aurobindo is not indicated for use in children.
Safety and effectiveness in children have not been established.

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

Mood alterations and depression
Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms and if these occur, the patient should be advised to seek medical advice.

Excipients:
Finasteride Aurobindo contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Finasteride Aurobindo contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per each tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions of clinical importance have been identified. Finasteride is metabolized primarily via, but does not appear to affect significantly, 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. Finasteride does not appear to affect significantly the cytochrome P450-linked drug metabolizing enzyme system. Compounds which have been tested in man have included propanolol, digoxin, glibenclamide, warfarin, theophylline and phenazone and no clinically meaningful interactions were found.

4.6 Fertility, pregnancy and lactation

Pregnancy
Finasteride Aurobindo is contraindicated for use in women when they are or may potentially be pregnant (see section 4.3).

Because of the ability of the 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 (see section 5.3).

Exposure to finasteride - risk to male fetus.
Women should not handle crushed or broken tablets of finasteride 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 section 6.6). Finasteride 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 from the semen in subjects receiving finasteride 5 mg/day. It is not known whether a male fetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. When the patient's sexual partner is or may potentially be pregnant, the patient is recommended to minimise exposure of his partner to semen.

Breastfeeding:
Finasteride Aurobindo is not indicated for use in women.
It is not known whether finasteride is excreted in human milk.

Fertility
Long-term data on fertility in humans are lacking, and specific studies in subfertile men have not been conducted. The male patients who were planning to father a child were initially excluded from clinical trials. Although, animal studies did not show relevant negative effects on fertility, spontaneous reports of infertility and /or poor seminal quality were received post-marketing. In some of these reports, patients had other risk factors that might have contributed to infertility.

4.7 Effects on ability to drive and use machines

There are no data to suggest that finasteride affects the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
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.

Tabulated list of adverse reactions

The adverse reactions reported during clinical trials and/or post-marketing use are listed in the table below. Frequency of adverse reactions is determined as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).
The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.

System Organ Class	Frequency: adverse reactions
Investigations	*Common:* decreased volume of ejaculate
Immune system disorders	*Unknown:* hypersensitivity reactions such as angioedema (including swelling of the lips, tongue, throat and face)
Psychiatric disorders	*Common:* decreased libido *Not known*: depression, decreased libido that continued after discontinuation of treatment and anxiety, suicidal ideation
Cardiac disorders	*Unknown:* palpitation
Hepatobiliary disorders	*Unknown:* increased hepatic enzymes
Skin and subcutaneous tissue disorders	*Uncommon:* rash *Unknown:* pruritus, urticaria
Reproductive system and breast disorders	*Common:* impotence *Uncommon:* ejaculation disorder, breast tenderness, breast enlargement Isolated cases of breast secretion have also been reported and, in association with gynaecomastia, the development of breast lumps, which were surgically removed in individual patients *Unknown*: testicular pain, hematospermia,sexual dysfunction (erectile dysfunction and ejaculation disorder) which may continue after discontinuation of treatment; male infertility and/or poor seminal quality.Normalization or improvement of seminal quality has been reported after discontinuation of finasteride

In addition following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4).

Combination therapy with doxazosin
The following undesirable effects have been reported more frequently when finasteride 5 mg was used together with doxazosin, an alpha-receptor blocker: asthenia 16.8% (placebo 7.1%), postural hypotension 17.8% (placebo 8.0%), dizziness 23.2% (placebo 8.1%) and ejaculation disorders 14.1% (placebo 2.3%).

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

Other long-term data

In a 7 year placebo-controlled trial that enrolled 18,882 healthy men ≥55 years of age with a normal digital rectal examination and a PSA ≤3.0 ng/mL, of whom 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving finasteride and 1147 (24.4%) men receiving placebo. In the finasteride group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%) men in the placebo group. Additional analyses suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride group may be explained by a detection bias due to the effect of finasteride on prostate volume. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2) at diagnosis. The clinical significance of the Gleason 7-10 data is unknown. This information may be relevant for men currently being treated with finasteride for BPH. Finasteride is not approved for reducing the risk of prostate cancer.

Breast Cancer
During the MTOPS study, which enrolled 3,047 men, during 4 to 6 years, to compare finasteride with placebo and an active comparator, 4 cases of male breast cancer were detected in men treated with finasteride. No cases of male breast cancer was detected in patients not treated with finasteride. In the PLESS study involving 3,040 men there were two cases of breast cancer reported in placebo-treated subjects but none in finasteride-treated subjects over a 4-year period. There was no difference in breast cancer rates reported in the PCPT study involving 18,882 men over a period of 7 years; one case was reported in the finasteride group and a second case in the placebo group.
Breast cancer has been reported in men taking finasteride 5 mg during the post-marketing period. The relation between the long-term use of finasteride and male breast cancer is still unknown.

Laboratory test findings
When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels are decreased in patients treated with finasteride (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via ADR Reporting, Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

No specific treatment of overdosage with Finasteride = is recommended.
Patients have received single doses of finasteride up to 400 mg and multiple doses up to 80 mg/day for three months without adverse effects. No specific treatment of overdosage with finasteride is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Testosteron 5 α-reductase inhibitors
ATC code: G04CB01

Mechanism of action

Finasteride is a synthetic 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme Type-II-5α-reductase. The enzyme converts testosterone into the more potent androgen dihydrotestosterone (DHT). The prostate gland and, consequently, also the hyperplasic prostate tissue

are dependent on the conversion of testosterone to DHT for their normal function and growth. Finasteride has no affinity for the androgen receptor.

Clinical studies show a rapid reduction of the serum DHT levels of 70%, which leads to a reduction on prostate volume. After 3 months, a reduction of approx. 20% in the volume of the gland occurs, and the shrinking continues and reaches approximately 27% after 3 years. Marked reduction takes place in the periurethral zone immediately surrounding the urethra. Urodynamic measurements have also confirmed a significant reduction of detrusor pressure as a result of the reduced obstruction. Significant improvements in maximum urinary flow rate and symptoms have been obtained after a few weeks, compared with the start of treatment. Differences from placebo have been documented at 4 and 7 months, respectively.

All efficacy parameters have been maintained over a 3-year follow-up period.

Effects of four years treatment with finasteride on incidence of acute urine retention need for surgery, symptom-score and prostate volume:

In clinical studies of patients with moderate to severe symptoms of BPH, an enlarged prostate on digital rectal examination and low residual urinary volumes, finasteride reduced the incidence of acute retention of urine from 7/100 to 3/100 over four years and the need for surgery (TURP or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA symptom score (range 0-34), a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

Initial clinical testing of finasteride (5 mg/day) in patients with BPH symptoms and prostate enlargement, identified via digital rectal examination, took place in two one-year, placebo-controlled, randomised, double-blind, phase III studies and in their five-year, open-label extension studies. The additional five years of treatment was completed by 234 out of the 536 patients who had been randomly assigned to treatment with finasteride (5 mg/day) in the double-blind studies; evaluation took place using the data from these 234 patients. The efficacy endpoints were symptom score, maximum urinary flow rate and prostate volume.

Furthermore, finasteride 5 mg was tested in the finasteride Long-Term Efficacy and Safety Study (PLESS), a four-year, double-blind, randomised, placebo-controlled, multicentre study. This study evaluated the effects of therapy with finasteride (5 mg/day) on the symptoms of BPH and BPH-related urological events (surgical intervention [e.g. transurethral resection of the prostate, TURP, or prostatectomy] or acute urinary retention requiring catheterisation). A total of 3,040 patients (age: 45-78 years), with moderate to severe BPH symptoms and prostate enlargement identified via digital rectal examination, were randomly assigned to treatment with finasteride (n = 1,524) or placebo (n = 1,516); 3,016 patients were evaluable. A total of 1,883 patients completed the four-year study (1,000 in the finasteride group and 883 in the placebo group). Also tested were the effects on maximum urinary flow rate and prostate volume.

<u>Effect on acute urinary retention and the need for surgical interventions</u>
In the four-year PLESS study, surgical intervention or catheterisation due to acute urinary retention was required in 13.2% of patients on placebo compared with 6.6% of patients on finasteride 5 mg, which demonstrated that, within a four-year period, administration of finasteride 5 mg reduced the risk of surgical intervention or acute urinary retention by 51% overall. With finasteride 5 mg, the risk of surgical intervention fell by 55% (10.1% for placebo vs. 4.6% for finasteride 5 mg) and the risk of acute urinary retention was reduced by 57% (6.6% for placebo vs. 2.8% for finasteride 5 mg). This risk reduction was evident even at the initial follow-up at four months and was maintained throughout the entire four-year duration of the study.

<u>Effect on symptom score</u>
In the two one-year phase III studies, a reduction in mean symptom score from baseline was found as

early as within week 2. After seven and ten months, a significant improvement in symptoms was found in these studies, compared to findings with placebo. In some cases, improvement of urological symptoms occurred very early on; however, a six-month treatment period was generally required to determine favourable effects in terms of a symptomatic improvement. The improvement in BPH symptoms was maintained during the first study year and during the five-year extension study.

In the four-year PLESS study, patients at baseline were suffering from moderate to severe symptoms (on average, about 15 points on a scale of 0 – 34). In those patients whose therapy was continued throughout the entire duration of the four-year study, finasteride 5 mg improved the symptom score by 3.3 points compared with 1.3 points ($p < 0.001$) for placebo. An improvement in symptom score in patients treated with finasteride 5 mg could be seen even within the first year and this improvement continued up to the fourth year. In those patients on placebo, although there was an improvement in symptom score in some cases, this was followed by subsequent deterioration. The greatest improvement in symptom score was mostly found in patients presenting with moderate to severe symptoms at study baseline.

Effect on maximum urinary flow rate
In the two one-year phase III studies, a significant increase in maximum urinary flow rate from baseline was found as early as within week 2. In the fourth and seventh months of these studies, a significant increase in maximum urinary flow rate was observed, compared to findings with placebo. This effect was maintained during the first study year and during the five-year extension study.

In the four-year PLESS study, a clear difference between the treatment groups was found from month 4 onwards in favour of finasteride 5 mg in terms of maximum urinary flow rate. This difference was maintained throughout the entire study. At study baseline, the mean maximum urinary flow rate in both treatment groups was around 11 ml/sec. In those patients whose therapy was continued throughout the entire duration of the study and for whom evaluable urinary flow data were available, the maximum urinary flow rate increased by an average of 1.9 ml/sec with finasteride 5 mg, compared with 0.2 ml/sec for placebo.

Effect on prostate volume
In the two one-year phase III studies, mean prostate volume at study baseline was 40 – 50 cm^3. In both studies, a significant reduction in prostate volume both compared to baseline and versus placebo was found as early as the initial follow-up after three months. This effect was maintained during the first study year and during the five-year extension study. In the four-year PLESS study, prostate volume was investigated at yearly intervals in a subset of patients (n = 284) via magnetic resonance imaging. In those patients on treatment with finasteride 5 mg, there was found to be a reduction in prostate volume both compared to baseline and placebo throughout the entire four-year course of the study. Among the patients in this subset whose therapy was continued over the entire study duration, finasteride 5 mg reduced prostate volume by 17.9% (from 55.9 cm^3 at baseline to 45.8 cm^3 after four years), whilst prostate volume increased by 14.1% in the placebo group (from 51.3 cm^3 to 58.5 cm^3) ($p < 0.001$).

Prostate volume as a predictor for therapeutic success
A meta-analysis from seven double-blind, placebo-controlled one-year studies of similar design, with a total of 4,491 patients with symptomatic BPH, showed that, in patients treated with finasteride 5 mg, the degree of maximum urinary flow rate were greater in patients with an enlarged symptomatic improvement and the increase in prostate (from about 40 cm^3).

Medical therapy of prostatic symptoms
The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent

urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34(p=0.002), 39 (p<0.001), and 67% (p<0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67(p=0.011), 31 (p=0.296), and 79% (p=0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.

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

In this study the safety and tolerability profile of combined treatment was broadly similar to the profile of each of the drugs taken separately. However, undesirable effects concerning the "nervous system" and "uro-genital system" organ classes were observed more frequently when the two drugs were used in combination (see section 4.8).

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 cc (SE)] in total gland size, largely accounted for by a reduction [6.2 3 cc] 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.

5.2 Pharmacokinetic properties

Absorption:

The oral bioavailability of finasteride is approx. 80%, relative to an intravenous reference dose, and is not affected by food. Peak plasma concentrations are reached approx. 2 hours after drug intake, and absorption is complete after 6-8 hours.

Distribution:
Binding to plasma proteins is approx. 93%. Clearance and volume of distribution are approx. 165 ml/min (70-279 ml/min) and 76 l (44-96 l), respectively. Accumulation of small amounts of finasteride is seen on repeated administration. After a daily dose of 5 mg the lowest steady-state concentration of finasteride has been calculated to be 8-10 ng/ml, which remains stable over time.

Biotransformation:
Finasteride is metabolised in the liver. Finasteride does not significantly affect the cytochrome P 450 enzyme system. Two metabolites with low 5α-reductase-inhibiting effects have been identified.

Elimination:

In the elderly, the elimination rate of finasteride is somewhat decreased. The plasma half-life averages increases with age from approximately 6 hours in men aged 18-60 years (range 4-12 hours) to 8 hours in men aged more than 70 years of age (range 6-15 hours). This is of no clinical significance and does not warrant a reduction in dosage.

After administration of radioactively labelled finasteride, approx. 39% (32-46%) of the given dose is excreted in the urine in the form of metabolites. Virtually no unchanged finasteride is recovered in the urine. Approximately 57% (51-64%) of the total dose is excreted in the faeces.

In patients with chronic renal impairment, whose creatinine clearance ranged from 9-55 ml/min, the disposition of a single dose of ^{14}C-finasteride was not different from that in healthy volunteers (see section 4.2). Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. Dosage adjustment in non-dialysed patients with renal impairment is not necessary.

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 to the CSF. Finasteride has also been recovered in the seminal fluid of subjects receiving 5 mg/day Finasteride. The amount of finasteride in the seminal fluid was 50 to 100 fold less than the dose of finasteride (5 mcg) that had no effect on circulating DHT levels in adult males.

5.3 Preclinical safety data

The oral LD50 of finasteride in male and female mice is approximately 500 mg/kg. The oral LD50 of finasteride in female and male rats is approximately 400 and 1000 mg/kg, respectively.

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman could be exposed via semen. The reproductive toxicity is believed to be mediated via the intended inhibition of 5α-reductase. Taken into account the species enzyme difference in sensitivity to finasteride inhibition the margin of pharmacological exposure would be about 4 times. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated mount of finasteride in 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."

Carcinogenesis and Mutagenesis

No evidence of a tumorigenic effect was observed in a study in rats receiving up to 320 mg/kg/day of finasteride for 24 months (3,200 times the recommended human dose).

In a 19-month carcinogenicity study in mice, a statistically significant ($p \leq 0.05$) increase in the frequency of testicular Leydig cell adenomas was observed at a dosage of 250 mg/kg/day (2,500 times higher than the recommended human dose); no adenomas were observed in mice given 2.5 or 25 mg/kg/day (25 and 250 times the recommended human dose, respectively).

No evidence of mutagenicity was observed in in vitro bacterial mutagenesis, mammalian cell mutagenesis, or in vitro alkaline elution assays. 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 are 4,000-5,000 times higher than the maximum plasma concentrations obtained in man with a total dose of 5 mg. Furthermore, the concentrations used in in vitro studies (450-550 µmol) cannot be achieved in a biological system. In an in vivo chromosome aberration assay in mice, no treatment related increase in chromosome aberrations was observed when finasteride was administered at the highest tolerated dose (250 mg/kg/day, 2,500 times the recommended human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Cellulose, microcrystalline (Grade-101)
Sodium starch glycolate (Type A)
Starch pregelatinised (maize)
Docusate sodium
Magnesium stearate

Film-coating:
Hydroxypropyl cellulose
Hypromellose (6 cP)
Titanium dioxide (E171)
Talc
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium foil blister

Pack sizes : 10, 20, 28, 30, 50, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Women who are pregnant or may become pregnant must not handle crushed or broken Finasteride tablets because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus. Finasteride tablets have a film coating, which prevents contact with the active ingredient provided that the tablets have not been broken or crushed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malt

8. MARKETING AUTHORISATION NUMBER(S)

MA807/10001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 14th September 2016
Date of renewal: 28th July 2022

10. DATE OF REVISION OF THE TEXT

17th July 2025