

FINASTERIDE 5 MG FILM-COATED TABLETS
PL 20915/0010
PL 20915/0011

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FINASTERIDE 5 MG FILM-COATED TABLETS

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LAY SUMMARY

The MHRA granted APS Alster Pharma Services GmbH Marketing Authorisations (licences) for the medicinal product Finasteride 5 mg film-coated tablets (PL 20915/0010 and PL 20915/0011). These are prescription only medicines (POM) for the treatment of benign prostatic hyperplasia (BPH), a condition caused by the prostate gland growing too big and obstructing the flow of urine from the bladder.

Finasteride 5 mg film-coated tablets contain the active ingredient finasteride which is an alpha-reductase inhibitor.

The test product was considered to be the same as the original product Proscar[®] (Merck Sharp & Dohme Ltd) based on the bioequivalence study submitted.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Finasteride 5 mg film-coated tablets outweigh the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal product Finasteride 5 mg film-coated tablets (PL 20915/0010 and PL 20915/0011) to APS Alster Pharma Services GmbH on 06 February 2007. The products are prescription only medicines.

Two identical strengths of finasteride were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic products of Proscar® (Merck Sharp & Dohme Ltd). The reference product has been authorised in the UK since May 1992 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient finasteride and are indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate, to cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH and to reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

Finasteride is an active testosterone 5-alpha-reductase inhibitor. It is used as a surgical alternative for the treatment of BPH. It reduces dihydrotestosterone concentrations in blood and consequently the size of the prostate by a combination of atrophy and apoptosis, improving urinary flow. Finasteride significantly reduces serum prostate specific antigen (PSA) concentrations by 40% to 70% in patients with BPH. However, mean free-to-total PSA is unaffected by the drug.

The applications were submitted at the same time and both depend on the bioequivalence study that compares the applicant's products with the reference product Proscar® (Merck Sharp & Dohme Ltd). Consequently, all sections of the Scientific Discussion refer to both applications.

PHARMACEUTICAL ASSESSMENT

COMPOSITION

The products are formulated as film-coated tablets containing 5mg of the active pharmaceutical ingredient finasteride. The excipients present are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, lauroyl macroglycerides, sodium starch glycolate type A, magnesium stearate and purified water. In addition, hypromellose 6cps., titanium dioxide (E 171), indigocarmine-lake (E 132) and macrogol 6000 are present in the coating.

The tablets are presented in aluminium-foil sealed PVC or aluminium blisters in packs of 7, 14, 15, 20, 28, 30, 50, 60, 98 and 100 tablets. Tablets are also available in HDPE containers with tamper evident LDPE screw caps, in packs of 100, 250 and 500 tablets.

DRUG SUBSTANCE

Finasteride

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopeia specification is provided for finasteride.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for one batch and comply with the proposed specification.

Finasteride is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 2 years when stored in the proposed packaging at 25°C and 60% relative humidity.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards with the exception of indigocarmine-lake (E 132) which is tested as per an acceptable in-house specification.

Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the

production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Dissolution profiles

Dissolution profiles for the drug product were found to be similar to the reference product.

Manufacture

A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory process validation has been carried out.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification.

Container Closure System

Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability data support the proposed shelf-life of 36 months with no special storage conditions.

Bioequivalence/bioavailability

Refer to the clinical assessment report.

SPC, PIL and Labels

The SPC, PIL and labels are pharmaceutically acceptable.

CONCLUSION

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products.

It is recommended that Marketing Authorisations should be granted for these applications.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

This is a generic abridged application for film-coated tablets containing 5mg finasteride.

The applications are submitted under the provisions of Directive 2001/83/EC Article 10.1, claiming that Finasteride 5 mg film-coated tablets are generic products of Proscar ® (Merk Sharp and Dome Ltd) which was authorised in the UK in May 1992.

INDICATIONS

The applicant has submitted the following:

Finasteride 5 mg film-coated tablets are indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an 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 the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

These indications are consistent with those for the innovator product.

DOSE AND DOSE SCHEDULE

The proposed dose and dose schedule for this product to be used for the above indications is 5 mg daily and is consistent with the innovator product.

CLINICAL PHARMACOLOGY

Bioavailability/bioequivalence

A bioequivalence study has been submitted which was conducted to principles of Good Clinical Practice (GCP). This was an open-label, laboratory-blind, single dose, two period randomised crossover study conducted in healthy adult male volunteer subjects.

Study design

Thirty-six subjects were screened and enrolled in the bioequivalence study. One subject withdrew for personal reasons prior to the second treatment phase.

The unit doses were one tablet of APS Finasteride 5 mg film-coated tablets (test) and Proscar ® 5 mg tablets (reference).

After randomisation, the relevant medication was administered at controlled fasting conditions on two occasions of 36 hours duration separated by a washout period of at least 14 days. Blood samples were obtained at 19 time points after dosing and finasteride content was analysed by LC-MS/MS (LLOQ 0.09 ng/ml).

According to the Committee for Proprietary Medicinal Products Note for Guidance on the Investigation of Bioavailability and Bioequivalence the single dose study is sufficient for Finasteride 5 mg film-coated tablets. The study was of an appropriate design.

Results

The results are summarised in the following table:

Parameter	Finasteride 5 mg tablets (test) A	Proscar ® 5 mg tablets (reference) B	90% geometric CI Ratio A/B %
AUC _{0-inf} ng*h/ml	304	299	97.4 to 106
AUC _{0-t} ng*h/ml	294	290	97.2 to 106
C _{max} ng/ml	44.1	45.5	92.2 to 102
T _{max} h	1.33	1.33	

Discussion

The results for all parameters fall within the required 90% confidence interval limits of 80 to 125% and it can be concluded that Finasteride 5 mg film-coated tablets are bioequivalent to Proscar ® tablets.

CLINICAL EFFICACY

No new efficacy data are presented in these applications and none are required.

CLINICAL SAFETY

No formal safety data are presented in these applications and none are required.

CLINICAL EXPERT REPORT

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

SPC, PIL and LABELS

The SPC, PIL and labels are acceptable.

CONCLUSIONS

The applicant has submitted a bioequivalence study which is of an appropriate design and demonstrates that Finasteride 5 mg film-coated tablets are bioequivalent to the reference product. Marketing Authorisations should be granted for these applications.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Finasteride 5 mg film-coated tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Finasteride 5 mg film-coated tablets and Proscar ® (Merck Sharp & Dohme Ltd).

No new or unexpected safety concerns arise from these applications.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the reference product are interchangeable. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the Marketing Authorisation applications on 15 June 2004.
- 2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 08 July 2004.
- 3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 07 March 2005, 18 August 2005, 07 December 2005 and 23 June 2006, and further information relating to the clinical dossiers on 07 March 2005.
- 4 The applicant responded to the MHRA's requests, providing further information on 20 July 2005, 28 October 2005, 07 November 2006 and 12 January 2007 for the quality sections, and again on 08 December 2006 for the clinical sections.
- 5 The applications were determined on 06 February 2007.

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STEPS TAKEN AFTER AUTHORISATION – SUMMARY

Date submitted	Application type	Scope	Outcome
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of finasteride.

Excipient: 90.95 mg lactose monohydrate/film-coated tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Blue-coloured, biconvex, round, film-coated tablets marked 'F5'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

'Finasteride' is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an 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 the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

4.2 Posology and method of administration

The recommended adult dose is one 5 mg film-coated tablet daily, with or without food.

Finasteride 5 mg film-coated tablets are for oral use only and should be swallowed whole.

Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1 'Pharmacodynamic properties').

Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.

No dosage adjustment is required in the elderly or in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 ml/min).

There are no data available in patients with hepatic insufficiency.

'Finasteride' is contra-indicated in children.

4.3 Contraindications

Hypersensitivity to any component of this product; women who are or may potentially be pregnant; children.

4.4 Special warnings and precautions for use

General

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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'.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with 'Finasteride' and periodically thereafter. Generally, when PSA assays are performed 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 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. In 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 therapy with 'Finasteride'.

Percent free PSA (free to total PSA ratio) is not significantly decreased by 'Finasteride' and 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 is necessary.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically important drug interactions have been identified. 'Finasteride' does not appear to significantly affect the cytochrome P450-linked drug metabolising enzyme system. Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

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, H₂ antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy: 'Finasteride' is contra-indicated in women who are or may potentially be pregnant.

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

In animal developmental studies, dose-dependent development of hypospadias were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 Tg/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, transient nipple development and decreased anogenital distance, when given finasteride at doses below 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 5 α -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 5 I-reductase. It is for these reasons that 'Finasteride' is contra-indicated in women who are or may potentially be pregnant.

No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Exposure to finasteride -risk to male foetus

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 foetus (see 'Pregnancy'). '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 foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride.

Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue 'Finasteride'.

Lactation: 'Finasteride' 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

None reported.

4.8 Undesirable effects

'Finasteride' is well tolerated. In controlled clinical studies where patients received 5 mg of finasteride over periods of up to four years, the following adverse reactions were considered possibly, probably or definitely drug-related and occurred with a frequency greater than placebo and greater than or equal to 1%: impotence, decreased libido, ejaculation disorder, decreased volume of ejaculate; breast enlargement, breast tenderness and rash. There was no evidence of increased adverse experiences with increased duration of treatment with 'Finasteride' and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

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 events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%.

The following additional adverse experiences have been reported in post-marketing experience:

- hypersensitivity reactions, including pruritus, urticaria and swelling of the lips and face
- testicular pain.

Laboratory test findings

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 generally 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 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 'Special warnings and precautions for use', *Effects on prostate-specific antigen (PSA) and prostate cancer detection*.

No other difference was observed in patients treated with placebo or 'Finasteride' in standard laboratory tests.

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 of 'Finasteride' up to 80 mg/day for up to three months without any adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Finasteride (ATC code G04CB01), is a competitive inhibitor of human testosterone-5- α -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.

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.

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

5.2 Pharmacokinetic properties

After an oral dose of ^{14}C -finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine), and 57% of total dose was excreted in the faeces. Two metabolites have been identified which possess only a small fraction of the Type II 5 α -reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6-8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately six hours in men aged 18-60 years to eight hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

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. 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.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood-brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline
Lactose monohydrate
Magnesium stearate
Pregelatinised starch
Sodium starch glycolate type A
Lauroyl Macrogolglycerides
Hypromellose 6 cps.
Indigocarmine-lake (E 132)
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

None reported.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

There are no special storage instructions.

6.5 Nature and contents of container

1. PVC – Aluminium blister
2. Aluminium – Aluminium blister
3. HDPE bottles with LDPE closure

Pack sizes:

- 7, 14, 15, 20, 28, 30, 50, 60, 98, 100 film-coated tablets (as blister packs)
28x1, 30x1, 50x1, 98x1, 100x1 film-coated tablets (as unit dose blister)
7 film-coated tablets (blister packs as samples)
100, 250, 500 film-coated tablets (HDPE bottles)

6.6 Special precautions for disposal

There are no special instructions for use and handling.

7 MARKETING AUTHORISATION HOLDER

APS Alster Pharma Services GmbH
Neuer Jungfernstieg 6a
20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20915/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/02/2007

10 DATE OF REVISION OF THE TEXT

06/02/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg of finasteride.

Excipient: 90.95 mg lactose monohydrate/film-coated tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Blue-coloured, biconvex, round, film-coated tablets marked 'F5'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

'Finasteride' is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an 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 the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

4.2 Posology and method of administration

The recommended adult dose is one 5 mg film-coated tablet daily, with or without food.

Finasteride 5 mg film-coated tablets are for oral use only and should be swallowed whole.

Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1 'Pharmacodynamic properties').

Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.

No dosage adjustment is required in the elderly or in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 ml/min).

There are no data available in patients with hepatic insufficiency.

'Finasteride' is contra-indicated in children.

4.3 Contraindications

Hypersensitivity to any component of this product; women who are or may potentially be pregnant; children.

4.4 Special warnings and precautions for use

General

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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'.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with 'Finasteride' and periodically thereafter. Generally, when PSA assays are performed 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 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. In 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 therapy with 'Finasteride'.

Percent free PSA (free to total PSA ratio) is not significantly decreased by 'Finasteride' and 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 is necessary.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically important drug interactions have been identified. 'Finasteride' does not appear to significantly affect the cytochrome P450-linked drug metabolising enzyme system. Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

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, H₂ antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Pregnancy: 'Finasteride' is contra-indicated in women who are or may potentially be pregnant.

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

In animal developmental studies, dose-dependent development of hypospadias were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 Tg/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, transient nipple development and decreased anogenital distance, when given finasteride at doses below 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 5 α -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 5 I-reductase. It is for these reasons that 'Finasteride' is contra-indicated in women who are or may potentially be pregnant.

No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Exposure to finasteride -risk to male foetus

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 foetus (see 'Pregnancy'). '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 foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride.

Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue 'Finasteride'.

Lactation: 'Finasteride' 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

None reported.

4.8 Undesirable effects

'Finasteride' is well tolerated. In controlled clinical studies where patients received 5 mg of finasteride over periods of up to four years, the following adverse reactions were considered possibly, probably or definitely drug-related and occurred with a frequency greater than placebo and greater than or equal to 1%: impotence, decreased libido, ejaculation disorder, decreased volume of ejaculate; breast enlargement, breast tenderness and rash. There was no evidence of increased adverse experiences with increased duration of treatment with 'Finasteride' and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

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 events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%.

The following additional adverse experiences have been reported in post-marketing experience:

- hypersensitivity reactions, including pruritus, urticaria and swelling of the lips and face
- testicular pain.

Laboratory test findings

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 generally 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 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 'Special warnings and precautions for use', *Effects on prostate-specific antigen (PSA) and prostate cancer detection*.

No other difference was observed in patients treated with placebo or 'Finasteride' in standard laboratory tests.

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 of 'Finasteride' up to 80 mg/day for up to three months without any adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Finasteride (ATC code G04CB01), is a competitive inhibitor of human testosterone-5- α -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.

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.

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

5.2 Pharmacokinetic properties

After an oral dose of ^{14}C -finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine), and 57% of total dose was excreted in the faeces. Two metabolites have been identified which possess only a small fraction of the Type II 5 α -reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6-8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately six hours in men aged 18-60 years to eight hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

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. 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.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood-brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

5.3 Preclinical safety data

No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline
Lactose monohydrate
Magnesium stearate
Pregelatinised starch
Sodium starch glycolate type A
Lauroyl Macrogolglycerides
Hypromellose 6 cps.
Indigocarmine-lake (E 132)
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

None reported.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

There are no special storage instructions.

6.5 Nature and contents of container

1. PVC – Aluminium blister
2. Aluminium – Aluminium blister
3. HDPE bottles with LDPE closure

Pack sizes:

- 7, 14, 15, 20, 28, 30, 50, 60, 98, 100 film-coated tablets (as blister packs)
28x1, 30x1, 50x1, 98x1, 100x1 film-coated tablets (as unit dose blister)
7 film-coated tablets (blister packs as samples)
100, 250, 500 film-coated tablets (HDPE bottles)

6.6 Special precautions for disposal

There are no special instructions for use and handling.

7 MARKETING AUTHORISATION HOLDER

APS Alster Pharma Services GmbH
Neuer Jungfernstieg 6a
20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 20915/0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/02/2007

10 DATE OF REVISION OF THE TEXT

06/02/2007

PATIENT INFORMATION LEAFLET

PLEASE READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TO TAKE YOUR TABLETS, EVEN IF YOU HAVE JUST HAD A REPEAT PRESCRIPTION. SOME OF THE INFORMATION IN YOUR PREVIOUS LEAFLET MAY HAVE CHANGED.

Keep this leaflet. You may want to read it again.
THIS MEDICINE IS FOR USE ONLY IN MEN

FINASTERIDE Film-coated Tablets 5 mg
(finasteride)

WHAT IS IN YOUR TABLETS?

Active ingredient

The active ingredient in 'Finasteride' is finasteride. 'Finasteride' is available as blue, biconvex, round film-coated tablets marked "F5", each containing 5 mg finasteride.

The following pack sizes are available:

7, 14, 15, 20, 28, 30, 50, 60, 98, 100 film-coated tablets (as blister packs)

28x1, 30x1, 50x1, 98x1, 100x1 film-coated tablets (as unit dose blister)

100, 250, 500 film-coated tablets (HDPE bottles)

Other ingredients

hypromellose 6 cps., lactose monohydrate, magnesium stearate, cellulose, microcrystalline, pregelatinised starch, lauroyl macroglycerides, sodium starch glycolate type A, titanium dioxide (E171), indigocarmine-lake (E 132), macrogol 6000.

HOW DOES 'FINASTERIDE' WORK?

'Finasteride' belongs to a group of medicines called 5-alpha reductase inhibitors. It works by shrinking the enlarged prostate gland in men.

MARKETING AUTHORISATION HOLDER AND MANUFACTURER

The Marketing Authorisation Holder is APS Alster Pharma Service GmbH, Neuer Jungfernstieg 6a, 20354 Hamburg, Germany. The tablets are manufactured by Actavis Ltd., Reykjavikurvegi 78, 222 Hafnarfjörður, Iceland and Intas Pharmaceuticals Ltd., Chinubhai Centre, Ashram Road, 380009 Ahmedabad, India.

WHY DO YOU NEED TO TAKE 'FINASTERIDE'?

Your doctor has prescribed 'Finasteride' for you because you have a condition known as benign prostatic hyperplasia or BPH. Your prostate gland, which is near your bladder, has become bigger and is making it more difficult for you to pass urine.

'Finasteride' helps to shrink the enlarged prostate and relieves your symptoms. 'Finasteride' will help reduce the risk of you developing a sudden inability to pass urine (known as acute urinary retention) and the need for surgery.

What is the prostate?

The prostate is a walnut-sized gland found only in men. It is located below the bladder and it surrounds the urethra, a tube that carries urine from the bladder out through the tip of the penis (see diagram). The prostate's main function is to produce fluid for semen, the fluid that carries sperm.

What is BPH?

BPH is a benign enlargement of the prostate gland which is common in men over 50 years old. Because the prostate is close to the bladder and surrounds part of the urethra, its enlargement may affect your ability to urinate. You may experience symptoms such as a need to urinate often, especially at night, a feeling that you must urinate right away, difficulty in starting to urinate, a weak or interrupted urinary stream, or a feeling that you cannot empty your bladder completely.

In some men, BPH can lead to serious problems, including urinary tract infections, and a sudden inability to pass urine at all as well as the need for surgery. For this reason, a man with symptoms of BPH should see his doctor.

ARE THERE PATIENTS WHO SHOULD NOT TAKE THESE TABLETS?

Yes, do not take these tablets if you are allergic to any of the ingredients.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

The condition for which 'Finasteride' is prescribed occurs only in men. The tablets must not be taken by women or by children.

WHAT ELSE SHOULD YOU KNOW BEFORE TAKING 'FINASTERIDE'?

BPH is not cancer and does not lead to cancer, but the two conditions can be present at the same time. Before starting you on 'Finasteride', it is likely that your doctor will perform some simple tests to check whether you have prostate cancer. Your doctor will evaluate your symptoms and their possible causes. Talk to your doctor if you have any questions.

'Finasteride' is for use in men only.

'Finasteride' can affect a blood test called PSA. If you have a PSA test done, tell your doctor that you are taking 'Finasteride'.

If the active ingredient in 'Finasteride' is absorbed by a woman who is pregnant with a male baby, it may affect the normal development of the baby's sex organs. Therefore, women who are or may potentially be pregnant, should not be exposed to 'Finasteride'. They should not take 'Finasteride'. In addition, they should not handle broken or crushed tablets or be exposed to the drug through sexual contact with a man taking 'Finasteride'. Therefore, if your sexual partner is or may potentially be pregnant, you must avoid exposing her to your semen which could contain a tiny amount of the drug - for example, by using a condom during sexual activity. If a woman

who is pregnant comes into contact with the active ingredient in 'Finasteride', a doctor should be consulted.

Whole 'Finasteride' Film-coated Tablets are coated to prevent contact with the active ingredient during normal handling.

Talk to your doctor if you have any questions.

CAN YOU TAKE 'FINASTERIDE' WITH OTHER MEDICINES?

'Finasteride' does not usually interfere with other medicines. However, you should always tell your doctor about all medicines you are taking or planning to take, including any obtained without a prescription.

HOW SHOULD YOU TAKE 'FINASTERIDE'?

You should take your tablets exactly as your doctor has told you. The dose is one film-coated tablet containing 5 mg finasteride to be taken by mouth once a day with or without food. In order to treat your symptoms and control your BPH effectively, it is important that you continue to take 'Finasteride' for as long as your doctor prescribes, even if you do not feel an immediate benefit. Some patients show early improvement in symptoms, but you may need to take 'Finasteride' for at least six months to see if it improves your symptoms. 'Finasteride' works best when taken long term.

WHAT IF YOU FORGET TO TAKE A TABLET OR TAKE TOO MANY?

If you miss a dose, just carry on with the next one as usual. Do not take an extra tablet to make up. If you take too many tablets by mistake, contact your doctor immediately.

WHAT UNWANTED EFFECTS COULD 'FINASTERIDE' HAVE?

Like any medicine, 'Finasteride' may have unintended or unwanted effects. These are uncommon and do not affect most men. Side effects due to 'Finasteride' may include: impotence (an inability to have an erection) or less desire to have sex. Some men may have changes or problems with ejaculation, such as a decrease in the amount of semen released during sex. This decrease in the amount of semen does not appear to interfere with normal sexual function. In some men, such side effects disappeared while the patient continued to take 'Finasteride'. If symptoms persist, they usually resolved on discontinuing 'Finasteride'.

In addition, some men may have breast swelling and/or tenderness. Some men have reported testicular pain and allergic reactions such as rash, itching, hives and swelling of the lips and face.

If you experience these or any other unusual symptoms, go and see your doctor promptly.

It will help if you make a note of what you experienced, when it started and how long it lasted.

HOW SHOULD YOUR TABLETS BE KEPT?

Keep your tablets out of the reach and sight of children.

There are no special storage instructions.

If you have been given a calendar pack, do not remove the tablets from the blister until you are ready to take the medicine.

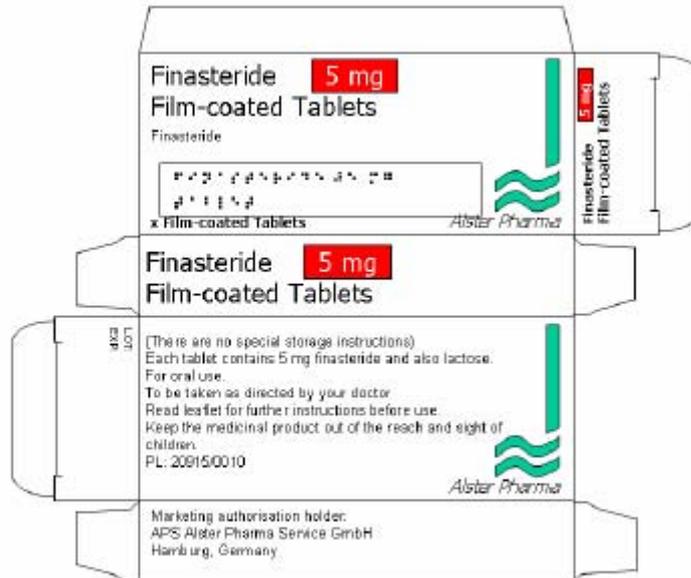
Do not take the tablets past the expiry date which is clearly marked on the pack.

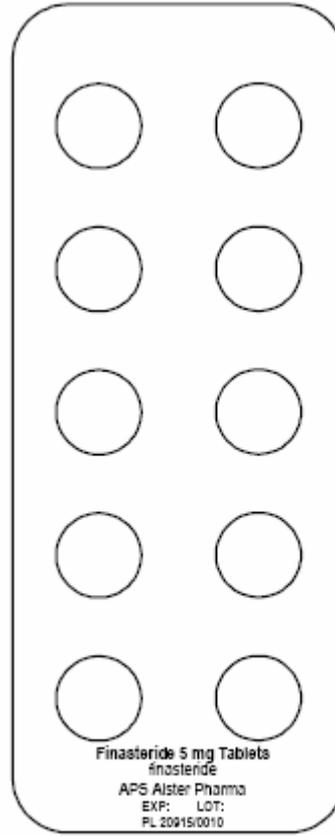
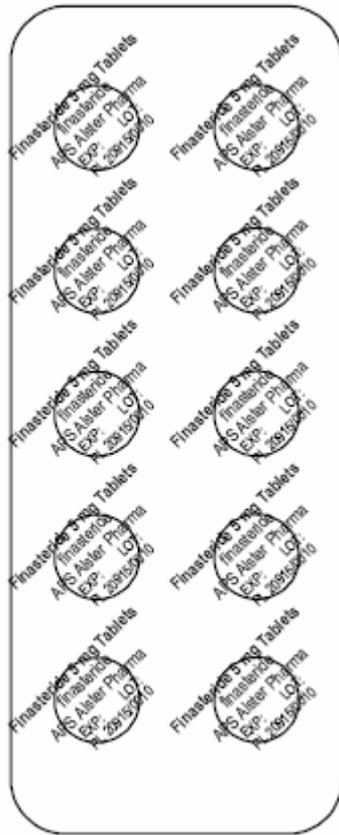
REMEMBER: This medicine is for you. Do not share it with anyone else. It may not suit them.
This leaflet was revised in May 2005.

HOW CAN YOU OBTAIN MORE INFORMATION ABOUT 'FINASTERIDE'?

This leaflet gives you the most important patient information about 'Finasteride'. If you have any questions after you have read it, ask your doctor or pharmacist, who will give you further information.

LABELLING





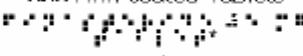
Each tablet contains 5 mg finasteride
and also lactose monohydrate.

LOT:
EXP:

PL20915/0010

Finasteride 5 mg
Film-coated Tablets

xxx Film-coated Tablets

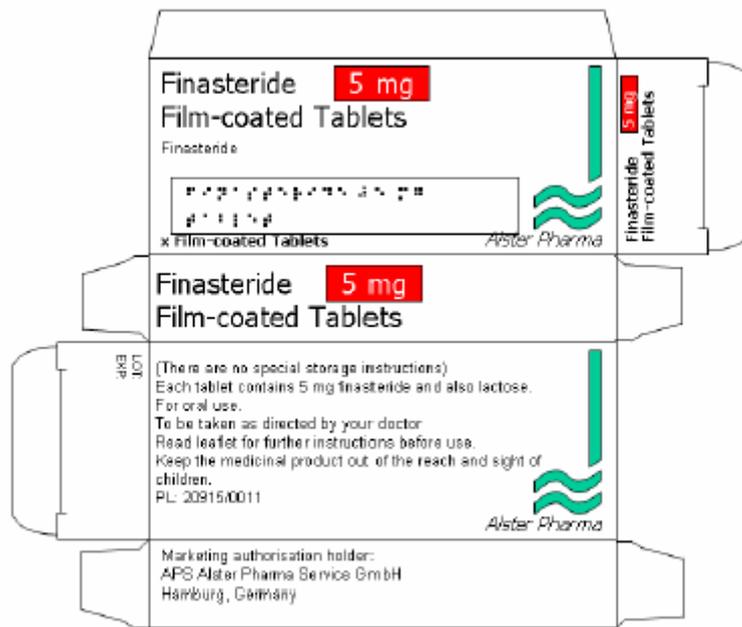


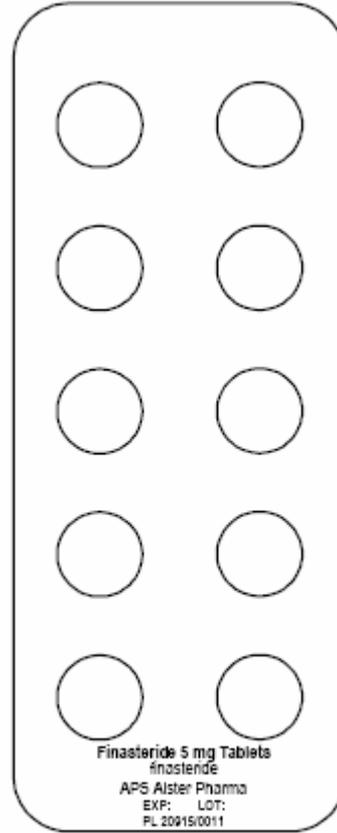
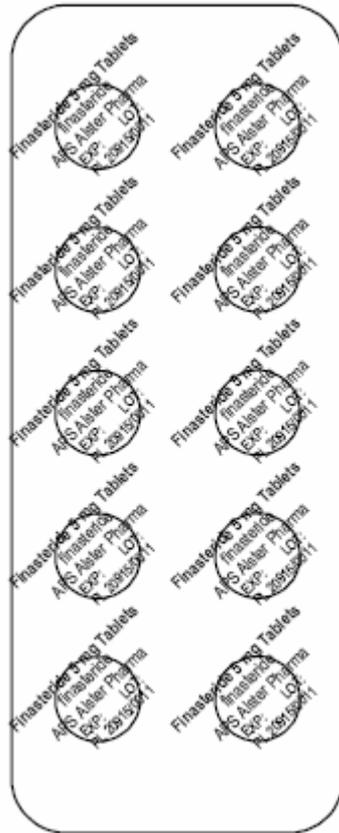
For oral use.
To be taken as directed by your doctor
Read leaflet for further instructions before use.
Keep this medicinal product out of the reach and sight of children.

Marketing authorisation holder:
APS Alster Pharma Service GmbH
Hamburg, Germany



Alster Pharma





Each tablet contains 5 mg finasteride
and also lactose monohydrate.

LOT:
EXP:

PL20915/0011

Finasteride 5 mg
Film-coated Tablets

xxx Film-coated Tablets
FINASTERIDE 5 mg
TABLETS *

For oral use.
To be taken as directed by your doctor.
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Keep this medicinal product out of the
reach and sight of children.
Marketing authorisation holder:
APS Alster Pharma Service GmbH
Hamburg, Germany

