

FINASTERIDE 5 MG TABLETS
PL 08608/0086-88

UKPAR

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FINASTERIDE 5 MG TABLETS
PL 08608/0086-88

LAY SUMMARY

The MHRA granted Olinka UK Limited Marketing Authorisations (licences) for the medicinal products Finasteride 5 mg Tablets (PL 08608/0086-88). This medicine is available by prescription-only (POM).

With advancing age some men suffer from enlargement of the prostate gland, causing them problems with passing urine. Finasteride works by reducing levels of the chemical that causes prostate enlargement, thus reducing the size of the enlarged prostate and relieving urinary symptoms.

Finasteride Tablets contain the active ingredient finasteride, which is an antiandrogen medicine.

The test product was considered the same as the original products Proscar 5 mg Tablets (Merck, Sharp and Dohme Limited) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Finasteride 5 mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

**FINASTERIDE 5 MG TABLETS
PL 08608/0086-88**

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 products Finasteride 5 mg Tablets (PL 08608/0086-88) on 23rd April 2007. The products are prescription-only medicines.

These are national applications for Finasteride 5 mg film-coated Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended, which have been shown to be generic medicinal products of the original, Proscar 5 mg Tablets first authorised to Merck, Sharp and Dohme in Austria in April 1992. The reference product has therefore been authorised in the EU for more than 10 years.

Finasteride is a competitive inhibitor of 5 α -reductase, a chemical that metabolises the conversion of testosterone into the more potent dihydrotestosterone. Enlargement of the prostate gland is dependant upon the conversion of testosterone to dihydrotestosterone within the prostate. Finasteride thus inhibits prostatic enlargement by reducing circulating and intraprostatic dihydrotestosterone.

Finasteride 5 mg Tablets are indicated for the treatment of benign prostatic hyperplasia

These applications were submitted at the same time and depend on the bioequivalence study comparing the applicant's 5 mg product with the reference product Proscar 5mg Tablets (Merck, Sharp and Dohme). Consequently, all sections of this Scientific Discussion refer to all three products.

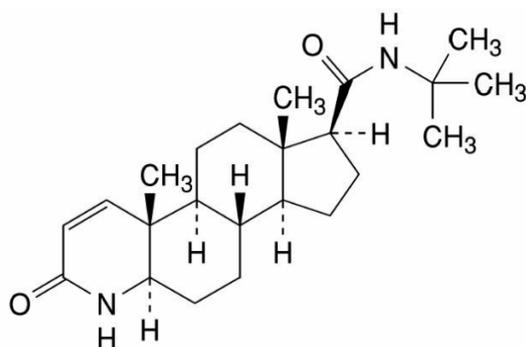
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Finasteride

INN:	Finasteride
Chemical Name:	(1) <i>N</i> -(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (Ph Eur name)
	(2) <i>N</i> -tert-Butyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
	(3) (5 α -17 β)- <i>N</i> -(1,1-Dimethylethyl)-3-oxo-4-azaandrost-1-ene-17- carboxamide
	(4) 17- β -(<i>N</i> -tert-butylcarbonyl)-4-aza-5 α -androst-1-en-3-one

Structure:



Molecular formula: $C_{23}H_{36}N_2O_2$

Molecular weight: 372.6

Physical form: White or almost white, crystalline powder

Solubility: Practically insoluble in water, freely soluble in ethanol and methylene chloride.

Chirality: The molecule is chiral.

Polymorphism: Finasteride exhibits polymorphism

An appropriate specification based on the European Pharmacopoeia has been provided.

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

Active finasteride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided for three batches and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, when stored in the appropriate packaging at 25°C and 60% relative humidity.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, pregelatinised starch, lauroyl macroglycerides (Gelucire 44/14), sodium starch glycolate (A), magnesium stearate, purified water, hypromellose 6cps, titanium dioxide, indigocarmine-lake (E132) and macrogol 6000. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of indigocarmine-lake (E132) which complies with the FDA (in the absence of a Ph Eur monograph, this is acceptable). Satisfactory certificates of analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin are lactose monohydrate and magnesium stearate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. A satisfactory TSE certificate of suitability has been provided for the supplier of magnesium stearate.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution and impurity profiles of the drug product were found to be similar to those for the reference product.

Manufacture

A detailed description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on three batches and the results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The product is presented in three types of packaging either blister composed of aluminium and polyvinyl chloride (PVC) or aluminium/aluminium blisters or high density polyethylene (HDPE) containers with tamper evident screw caps made of low density polyethylene (LDPE). Specifications and certificates of analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The product is packaged in sizes of 12, 28, 30 and 56 tablets for both blister types of packaging and sizes of 50, 75 and 100 tablets for the HDPE containers.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set with no specific storage conditions, which is satisfactory.

Patient Information Leaflet

This is satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product for the proposed product have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

These applications are generic medicinal products of Proscar 5 mg Tablets (Merck, Sharp and Dohme), which have been licensed within the EEA for over 10 years.

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

CLINICAL ASSESSMENT

BACKGROUND

Finasteride is an orally active testosterone 5-alpha-reductase inhibitor. It is used as a surgical alternative for treatment of benign prostatic hyperplasia (BPH). In patients with BPH, it reduces dihydrotestosterone concentrations in blood and consequently reduces prostatic volume and improves urinary flow. Finasteride reduces prostatic size by a combination of atrophy and apoptosis. Finasteride reduces detrusor pressure in patients with bladder outlet obstruction by BPH. Finasteride significantly reduces serum prostate specific antigen (PSA) concentrations by 40% to 70% in patients with symptomatic BPH. However, mean free-to-total PSA is unaffected by the drug.

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.

ASSESSOR'S COMMENT

The indications are consistent with those for the innovator product.

POSODOLOGY AND METHOD OF ADMINISTRATION

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

Finasteride can be administered alone or in combination with the alpha-blocker doxazosin.

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.

Assessor's comment

The posology is consistent with that for the innovator product.

TOXICOLOGY

No new data has been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Finasteride causes a reduction in prostatic volume by a combination of atrophy and apoptosis. Finasteride reduces detrusor pressure in patients with bladder outlet obstruction caused by BPH. Finasteride causes a significant reduction in serum prostate specific antigen (PSA) concentrations by 40 to 70 percent in patients with symptomatic BPH. However, mean free-to-total PSA is unaffected by the drug.

PHARMACOKINETICS

Finasteride is well absorbed from the gastrointestinal tract, with food slowing the rate but not the extent of absorption. The bioavailability is about 80% and the volume of distribution about 1 l/kg. Finasteride is extensively metabolised in the liver and eliminated mainly by bile to faeces. The elimination half-life ranges from 3 to 14 hours.

BIOEQUIVALENCE

The study was an open –label, laboratory-blind, single dose, two period randomised crossover study conducted in healthy adult male volunteers. Subjects were screened and enrolled, one subject discontinued for personal reasons. The unit doses were one tablet of 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 and finasteride content was analysed by LC-MS/MS (LLOQ 0.09 nanog/ml). The results are summarised in the following table.

Summary tables of the main study results (n = 35)

Parameter	Proscar® Reference		Finasteride Test		Mean Ratio (%)*	90% Confidence Interval (%)**	Intra Individual CV (%)
	Geometric Mean	Range	Geometric Mean	Range			
C _{max} (ng/ml)	44.4	26.1- 69.4	43.0	24.4- 70.7	96.9	92.2; 102	12
T _{max} # (hour)	1.33	1.00- 5.00	1.33	0.50- 3.00	0.88	-0.17; 0.33	
AUC last (ng h/ml)	278	159- 513	283	120- 488	102	97.2; 106	11
AUC ∞ (ng h/ml)	287	163- 528	292	126- 504	102	97.4; 106	10
T _{1/2,z} (hour)	5.20	2.79- 7.52	5.15	2.98- 8.57	99.0	96.2; 102	7

*F: Point estimate of “test/reference” mean ratio from analysis of log-transformed data.

** : 90% Conventional confidence interval for the “test/reference” mean ratio from analysis of variance of log-transformed data.

: Medians, ranges, nonparametric point estimate of “test/reference” median difference and corresponding confidence interval.

Assessor’s comment

According to the CPMP NfG on the investigation of bioavailability and bioequivalence (CPMP/QWP/EWP/1401/98) the single dose study is sufficient for finasteride 5 mg tablets. The study was of an appropriate design.

The results for all parameters fall within the required 90 % confidence interval limits of 80 to 120% and it can be concluded that Finasteride 5 mg tablets are bioequivalent to Proscar 5 mg tablets.

EFFICACY

No new data have been submitted and none are required.

SAFETY

No new data have been submitted and none are required.

CLINICAL OVERVIEW

The clinical overview was submitted by a suitably qualified person.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The summary of product characteristics is consistent with that for the most recent UK SPC for the innovator product Proscar and is acceptable.

PATIENT INFORMATION LEAFLET

The Leaflet submitted is consistent with that of the innovator product Proscar. There are no clinical points additional to those raised in the pharmaceutical assessment.

LABELLING

This is satisfactory.

APPLICATION FORM

This conformed to EC requirements and was satisfactory.

DISCUSSION

These are National applications for a marketing authorisation for finasteride 5mg film-coated tablets. The indications are consistent with those for the reference product, Proscar[®] (PL 00025/0279).

The applicant has submitted a bioequivalence study which, is of an appropriate design and demonstrates that the applicant's finasteride 5 mg tablets are bioequivalent to the reference product.

CONCLUSION

Product licences should be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

The important quality characteristics of Finasteride 5 mg Tablets is 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 Tablets and Proscar 5 mg Tablets (Merck, Sharp and Dohme).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Proscar tablets.

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 products and the innovator products are interchangeable. Extensive clinical experience with finasteride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

FINASTERIDE 5 MG TABLETS
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 10 th September 2004.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 7 th October 2004.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 15 th March 2005, and further information relating to the quality dossiers on 6 th April 2005, 24 th January 2006 and 31 st August 2006
4	The applicant responded to the MHRA's requests, providing further information on 1 st April 2005 for the clinical sections, and again on 1 st December 2005, 31 st August 2006, and 14 th January 2007 for the quality sections.
5	The applications were determined on 23 rd April 2007.

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
4 th June 2007	Label & Leaflet-Self Certification	To register new pack dimensions.	Approved on 4 th June 2007

FINASTERIDE 5 MG TABLETS

PL 08608/0086-88

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of finasteride

Excipients:

Each tablet contains 90.95 mg of lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

Film-coated, Blue, round biconvex tablets. Diameter 7mm. Marked "F5" on one side.

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

Route of administration:

Oral use

The recommended adult dose is one 5 mg tablet daily, taken orally with or without food.

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.

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.

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

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 metabolizing enzyme system.

Compounds which have been tested in man include propranol, 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 I-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 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, 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 I-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

Not relevant.

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%.

Other long-term data

In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 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%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%). Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of finasteride and tumors with Gleason scores of 7-10 is unknown.

Post Marketing Experience

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 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 '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

Pharmacodynamic group: Testosterone – 5-alpha reductase inhibitors, ATC code: G04C B01

Finasteride is a competitive inhibitor of human 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 randomized 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 ¹⁴C-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 I-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 ¹⁴C-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

Lactose monohydrate
Cellulose microcrystalline
Pregelatinised starch
Lauroyl macrogolglycerides
Sodium starch glycolate (type A)
Magnesium stearate

Film coat
Hypromellose 6 cps.
Titanium dioxide (E171)
Indigocarmine-lake (E 132)
Macrogol 6000

6.2 INCOMPATIBILITIES

Not Applicable

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. Al/PVC Blister, pack sizes; 12, 28, 30 and 56 Tablets
2. Al/Al Blister, pack sizes; 12, 28, 30 and 56 Tablets
3. HDPE container and a white LDPE cap, pack sizes; 50, 75 and 100 Tablets

Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Women should not handle crushed or broken finasteride tablets when they are or may potentially be pregnant (see 'Contra-indications, 'Pregnancy and lactation', *Exposure to finasteride - risk to male foetus*).

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited,
38/40 Chamberlayne Road,
London NW10 3JN,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08608/0086
PL 08608/0087
PL 08608/0088

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2007

10 DATE OF REVISION OF THE TEXT

20/04/2007

FINASTERIDE 5 MG TABLETS
PL 08608/0086-88
PATIENT INFORMATION LEAFLET



FINASTERIDE 5 MG TABLETS

PATIENT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Finasteride 5mg Tablets are and what they are used for
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The name of this medicine is Finasteride 5mg Tablets

- The active substance is finasteride. Each tablet contains 5mg of finasteride.
- The film coated tablets also contain lactose monohydrate, cellulose microcrystalline, pregelatinised starch, lauroyl macroglycerides, sodium starch glycolate (type A), magnesium stearate, hypromellose 6 cps., titanium dioxide (E171), indigocarmine-lake (E132) and macrogol 6000. They are supplied in blister packs of 12, 28, 30 and 56 tablets and bottles of 50, 75 and 100 tablets.
- The tablets are film-coated, blue, round biconvex tablets with a diameter of 7mm, marked "F5" on one side.

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1. WHAT FINASTERIDE 5 mg TABLETS ARE AND WHAT THEY ARE USED FOR

Finasteride 5mg Tablets act by shrinking the enlarged prostate gland in men. Your doctor has prescribed the medicine for you to treat a condition known as benign prostatic hyperplasia or BPH. The prostate gland which is near the bladder, has become enlarged and is making it more difficult to pass urine. Finasteride 5 mg tablets will help to relieve these symptoms and 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. The prostate's main function is to produce fluid for semen, the fluid that carries sperm.

What is Benign Prostatic Hyperplasia (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.

2. BEFORE YOU TAKE FINASTERIDE

Do not take Finasteride 5mg Tablets if you are hypersensitive to finasteride or any of the other ingredients of Finasteride 5 mg tablets.

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 5 mg tablets are prescribed occurs only in men. The tablets must not be taken by women or by children.

Taking Finasteride 5mg Tablets with other medicines

Finasteride 5 mg tablets do not usually interfere with other medicines. However, you should always inform your doctor or pharmacist if you are taking or have recently taken any other medicines even if not prescribed.

What else you should know before taking Finasteride 5 mg Tablets

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 5 mg tablets are for use in men only.

Finasteride 5 mg tablets can affect a blood test called PSA. If you have a PSA test done, tell your doctor you are taking Finasteride 5 mg tablets.

If the active ingredient 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 5 mg tablets. They should not take Finasteride 5 mg tablets. In addition, they should not handle broken or crushed tablets or be exposed to the drug through sexual contact with a man taking Finasteride 5 mg tablets.

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 in contact with the active ingredient finasteride, a doctor should be consulted. Whole Finasteride 5 mg tablets are coated to prevent contact with the active ingredient during normal handling.

Talk to your doctor if you have any questions.

3. HOW TO TAKE FINASTERIDE 5mg TABLETS

Always take Finasteride 5 mg tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. The usual dose is one 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 5 mg tablets for as long as your doctor prescribes, even if you do not feel an immediate benefit. Some patients show early improvements in symptoms, but you may need to take Finasteride 5 mg tablets for at least six months to see if it improves your symptoms. Finasteride works best when it is taken long term.

Your doctor may prescribe Finasteride 5 mg tablets along with another medicine called doxazosin to help you control your BPH.

If you take more FINASTERIDE 5mg Tablets than you should:

If you have taken too many tablets by mistake, contact your doctor immediately.

If you forget to take FINASTERIDE 5mg Tablets

If you miss a dose, just carry on with the next one as usual. Do not take a double dose to make up for forgotten individual doses.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Finasteride 5mg Tablets can have side 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 5 mg tablets. If symptoms persist, they usually resolved on discontinuing Finasteride 5 mg tablets.

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.

A large scale clinical trial was conducted in which men were taking tablets containing the active ingredient finasteride or placebo for 7 years to study the prevention of prostate cancer (finasteride is not licensed for this treatment). The results showed that the number of men who developed prostate cancer was lower in the group treated with finasteride. However the number of men with a high score in a tumour grading system was higher in those men treated with finasteride than in men treated with placebo. The relationship between long-term use of finasteride and tumours of this kind is unknown.

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

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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING FINASTERIDE 5mg TABLETS

Keep out of the reach and sight of children

There are no special storage instructions

Do not use after the expiry date stated on the carton. Unused tablets should be taken back to the pharmacist for safe disposal.

This leaflet was last revised in April 2006

FINASTERIDE 5 MG TABLETS
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LABELS

