

**FINASTERIDE 5MG TABLETS
(FINASTERIDE)**

PL 29412/0001

UK Public Assessment Report

TABLE OF CONTENTS

Lay Summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 14
Summary of Product Characteristics	Page 15
Product Information Leaflet	Page 22
Labelling	Page 24

FINASTERIDE 5MG TABLETS
(FINASTERIDE)

PL 29412/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Hikma Limited a Marketing Authorisation (licence) for the medicinal product Finasteride 5mg Tablets (PL 29412/0001) on 4th March 2008. This is a prescription-only medicine (POM), used in the treatment and control of benign (not cancerous) enlargement of the prostate.

Finasteride 5mg Tablets contain the active ingredient finasteride, which belongs to a group of medicines called 5-alpha reductase inhibitors. 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.

The test product was considered to be a generic version of the reference product Proscar 5mg Tablets (Merck Sharp and Dohme Limited) based on data submitted by Hikma Limited.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Finasteride 5mg Tablets outweigh the risk; hence a Marketing Authorisation (MA) has been granted.

FINASTERIDE 5MG TABLETS

(FINASTERIDE)

PL 29412/0001

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 9
Clinical assessment	Page 10
Overall conclusion and risk benefit assessment	Page 13

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Hikma Limited a Marketing Authorisation for the medicinal product Finasteride 5mg Tablets (PL 29412/0001) on 4th March 2008. The product is a prescription-only medicine (POM) indicated for the treatment and control of benign prostatic hyperplasia in order to cause regression of an enlarged prostate, improvement of urinary flow and improvement of other symptoms associated with BPH. It is also used to reduce the incidence of acute urinary retention and the need for BPH-related surgical procedures in patients with BPH.

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the innovator product, Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited) that was granted a UK licence on 27/05/1992.

The product contains the active ingredient finasteride. Finasteride is an orally active testosterone 5-alpha-reductase inhibitor. It is an azasteroid that inhibits the type-2 isoform of 5 α -reductase, the enzyme responsible for conversion of testosterone to the more active dihydrotestosterone, and therefore has anti-androgenic properties. 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. It also reduces detrusor pressure in patients with bladder outlet obstruction by BPH. It is given by mouth in a dose of 5mg daily. Response may be delayed and treatment for 6 months or more may be required to assess whether benefit has been achieved.

The application depends upon the bioequivalence study presented by the applicant comparing the test product Finasteride 5mg Tablets with the reference product Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited).

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

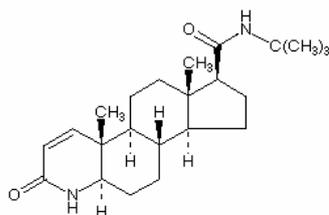
Finasteride

Nomenclature:

INN: Finasteride

Chemical name: N-tert-Butyl-3-oxo-4aza-5 α -androst-1-ene-17 β -carboxamide

Structure:



Molecular formula: C₂₃H₃₆N₂O₂

Molecular weight: 372.6

CAS No: 98319-26-7

Physical form: A white or almost white crystalline powder

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

Stereochemistry: The molecule has seven chiral centres. The active finasteride manufactured is a specific isomer with an optical rotation of 12.0° to 14.0°

The active substance, finasteride, is the subject of a European Pharmacopeia (EP) monograph.

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. Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which was set by the DMF holder and is in line with the European Pharmacopeia monograph specification. Additional tests are included to control particle size, polymorphic form, solubility in methanol, colour of solution, and bulk density.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Active finasteride is stored in appropriate packaging. It is packed in virgin food grade double transparent polythene bags, which are tied separately with a LDPE tamper proof fastener. The bags are packed into a fibre drum. Specifications and Certificates

of Analysis have been provided for the packaging material. The polythene bags in direct contact with the drug substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in miniature versions of the proposed packaging. This data demonstrates the stability of the drug substance and supports a retest period of 3 years at a storage condition of $25\pm 2^{\circ}\text{C}/60\pm 5\%\text{RH}$, when stored in the proposed packaging.

DRUG PRODUCT

Composition

The drug product is a direct-release film-coated tablet containing 5mg of the active substance. The tablets are blue, round, biconvex, with the marking "F5" on one side.

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, microcrystalline cellulose, pregelatinised starch, lauroyl macrogol glycerides, sodium starch glycollate, and magnesium stearate making up the tablet core; and hypromellose 6 cps, titanium dioxide (E171), indigo carmine lake (E132), and macrogol 6000 making up the film coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, apart from indigo carmine lake (E132) which complies with EU Directives and has FDA compliance. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. 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 that for human consumption.

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Dissolution profiles of Finasteride 5mg tablets were shown to be comparable with Proscar 5mg tablets.

Comparative impurity data were presented for Finasteride 5mg tablets and Proscar 5mg tablets. Impurity profiles for the drug product were found to be similar to those for the reference product, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and 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

Two types of primary packaging are proposed for the marketed product:

- (1) PVC/aluminium blister
- (2) Aluminium/aluminium blister

The tablets are packed in the blisters, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in carton pack sizes of 7, 14, 28, 30, 49, 50, 56, 98, 100, and 300 tablets. The MA Holder has stated that not all pack sizes will be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, which is satisfactory. There are no special storage instructions.

Bioequivalence Study

A bioequivalence study was submitted comparing the test product, Finasteride 5mg Tablets, to the innovator product, Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

Expert Report

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory.

Conclusion

The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. On this basis, and considering the bioequivalence data provided, the applicant's claim that Finasteride 5mg Tablets is a generic medicinal product of Proscar 5mg Tablets appears justified.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation may be granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Finasteride 5mg Tablets are indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate in order to cause regression of an enlarged prostate, improvement of urinary flow and improvement of other symptoms associated with BPH. They are also used to reduce the incidence of acute urinary retention and the need for BPH-related surgical procedures, such as transurethral resection of the prostate (TURP) and prostatectomy in patients with BPH. The indications are consistent with those for the innovator product.

POSODOLOGY AND METHOD OF ADMINISTRATION

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%. 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 Study

The bioequivalence study compared the test product, Finasteride 5mg Tablets (PL 29412/0001, Hikma Limited), to the reference product Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited), sourced from Germany. The study was of an appropriate design and was conducted to principles of good clinical practice.

The study was an open –label, laboratory-blind, single dose, two period randomised crossover study conducted in healthy adult male volunteers. 36 subjects were screened and enrolled, and data were analysed for thirty five, due to one withdrawing 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). The qualitative and quantitative composition of the UK and German products are the same. 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 0.09ng/ml).

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	

Bioequivalence was determined using the 90% confidence interval of the relative mean C_{max}, AUC 0-t and AUC_∞ of the test to reference formulation which should be 80% to 125%.

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 tablets are bioequivalent to Proscar 5 mg tablets.

EFFICACY

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

Efficacy is reviewed in the clinical expert report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

SAFETY

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

Safety is reviewed in the clinical expert report. The reference product is established and the main basis of the application depends upon the bioequivalence study.

EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The final SmPC is consistent with that for the innovator product, as well as with SmPCs harmonized through Europe, and it is acceptable.

Patient Information Leaflet

The final PIL is in line with the approved SmPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

DISCUSSION AND CONCLUSION

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test and reference products within general acceptance limits.

Sufficient clinical information has been submitted to support this application. When used as indicated, Finasteride 5mg Tablets has a favourable benefit-to-risk ratio. Therefore, a Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Finasteride 5mg 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Finasteride 5mg Tablets and the reference product Proscar 5mg Tablets (Merck Sharp and Dohme Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory and consistent with that for Proscar 5mg Tablets.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

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 innovator product are interchangeable. Extensive clinical experience with finasteride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**FINASTERIDE 5MG TABLETS
(FINASTERIDE)**

PL 29412/0001

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 18th February 2007
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 3rd April 2007
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 15th June 2007
- 4 The applicant responded to the MHRA's request, providing further information for the quality sections on 27th December 2007
- 5 The application was determined on 4th March 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Finasteride 5mg Tablets is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 5 mg 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

Blue, round biconvex 7mm film-coated with "F5" marking 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.

Finasteride 5 mg tablets should be administered in patients with an enlarged prostate (prostate volume above ca. 40 ml)

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Dosage in adults

The recommended dosage is one 5 mg tablet daily with or without food. The tablet should be swallowed whole and must not be divided or crushed (see section 6.6). Even though improvement can be seen with in a short time, treatment for at least 6 months may be necessary in order to determine objectively whether a satisfactory response to treatment has been achieved.

Dosage in Children

Finasteride is contra-indicated in children (see section 4.3).

Dosage in the elderly

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

Dosage in hepatic Insufficiency

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

Dosage in renal insufficiency

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to Finasteride or any of the excipients.
- Contra-indicated in women who are or may potentially become pregnant; children (see sections 4.4, 4.6 and 6.6).

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.
- Consultation of an urologist should be considered in patients treated with Finasteride
- Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with Finasteride.
- There is no experience in patients with liver insufficiency. Since Finasteride is metabolized in the liver (see section 5.2) caution is advised in patients with decreased hepatic function as the plasma levels of Finasteride may be increased in such patients
- This medicinal product contains lactose-monohydrate . Patients with rare hereditary problems of galactose, Lapp Lactase deficiency or glucosegalactose 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.

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. Digital rectal examination, and, if necessary, determination of prostate-specific-antigen (PSA) in serum should be carried out on patients prior to initiating therapy with finasteride and periodically during treatment to rule out prostate cancer. 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.

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.

Women who are pregnant or may become pregnant should not handle crushed or broken finasteride tablets because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. Finasteride tablets have a film coating which prevents contact with the active ingredient provided that the tablets have not been broken or crushed (see sections 4.6 and 6.6).

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

Finasteride is not indicated in women (see section 4.3)

Pregnancy: Finasteride is contra-indicated during pregnancy.

Because of the ability of 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 (see section 5.3).

Exposure to finasteride - risk to male foetus

Women who are pregnant or may be pregnant should not handle crushed or broken tablets of finasteride because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see section 6.6).

Finasteride tablets have a filmcoating which prevents contact with the active ingredient 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 is recommended to minimize exposure of his partner to semen.

Lactation: Finasteride Tablets are not indicated for use in women. It is not known whether finasteride is excreted in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no known data to show that finasteride influences the ability to drive and the capacity to operate machinery.

4.8 UNDESIRABLE EFFECTS

The most common adverse effects are impotence and reduced libido. These effects usually occur at the beginning of the treatment and in the majority of patients are of transient nature on continued treatment.

Reproductive System and breast disorders

Very Common ($\geq 1/10$)

- Impotence

Common ($> 1/100$, $< 1/10$):

- reduced libido
- reduced volume of ejaculate, breast tenderness breast enlargement
- ejaculation disorder (e.g. decrease volume of ejaculate)

Uncommon ($> 1/1000$, $1/100$):

- Testicular pain

Very rare ($< 1/10000$), including isolated reports:

- Breast secretion
- breast nodules

Skin and subcutaneous tissue disorders

- Common (> 1/100, < 1/10):
- Skin rash

Rare (> 1/10000, < 1/1000):

- Pruritus
- Urticaria

Nervous system disorders

- Somnolence

General disorders and administration site conditions

Rare (>1/10000, < 1/1000):

- Hypersensitivity reactions such as swelling of the face and lips

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%. Besides adverse reactions related to "Nervous System Disorders" were also observed with greater frequency in patients receiving the combination (see table below)

System Organ Class	Placebo	Doxazosin	Finasteride	Finasteride + Doxazosin
	N= 737 N = 737	N = 756 N = 756	N = 768 N = 768	N = 786 N= 786
	%	%	%	%
Patients with one or more undesirable effect	46.4	64.9	52.5	73.8
General Disorders	11.7	21.4	11.6	21.5
<i>Asthenia</i>	7.1	15.7	5.3	16.8
Cardiac Disorders	10.4	23.1	12.6	22.0
<i>Hypotension</i>	0.7	3.4	1.2	1.5
<i>Orthostatic Hypotension</i>	8.0	16.7	9.1	17.8
Nervous System	16.1	28.4	19.7	36.3
<i>Dizziness</i>	8.1	17.7	7.4	23.2
<i>Reduced Libido</i>	5.7	7.0	10.0	11.6
<i>Somnolence</i>	1.5	3.7	1.7	3.1
Uro-genital Disorders	18.6	22.1	29.7	36.8
Ejaculation disorders	2.3	4.5	7.2	14.1
Breast enlargement	0.7	1.1	2.2	1.5
Impotency	12.2	14.4	18.5	22.6
<i>Other sexual abnormalities</i>	0.9	2.0	2.5	3.1

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. See section 4.4 (paragraph 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 synthetic 4-azasteroid, specific competitive inhibitor of the intracellular enzyme Type II 5 α -reductase. The enzyme converts testosterone into the more potent androgen, dihydrotestosterone (DHT). The prostate gland and, consequently, also the hyperplastic prostate tissue are dependent upon the conversion of testosterone to DHT for normal function and growth. Finasteride has no affinity for the androgen receptor.

Clinical studies show a rapid reduction of Serum DHT levels of 70%, which leads to a reduction in prostate volume. After 3 months, a reduction of approx. 20% in the volume of the gland occurs, and the shrinking continues and reaches approx 27% after 3 years. Marked reduction takes place in the periurethral Zone immediately surrounding the Urethra. Urodynamic measurements have also confirmed a significant reduction of detrusor pressure as a result of the reduced obstruction.

Significant improvements in maximum urinary flow rate and symptoms have been obtained after a few weeks, compared with the stand of treatment. Differences from Placebo have been documented at 4 and 7 months, respectively.

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

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

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

5.2 PHARMACOKINETIC PROPERTIES*Absorption:*

The bioavailability of finasteride is approximately 80%. Peak plasma concentrations are reached approximately two hours after drug intake, and absorption is complete after 6-8 hours.

Distribution:

Binding to plasma proteins is approximately 93%.

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

Biotransformation:

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

Elimination:

The plasma half-life averages six hours (4 -12 hours) (in men > 70 years of age, 8 hours, range 6-15 hours). After administration of radioactively labeled Finasteride, approx 39% (32-46%) of the given is excreted in the urine. Approximately 57% (51-64%) of the total dose is excreted in the faeces.

In patients with impaired renal function (creatinine clearance as low as 9ml/min), no changes in the elimination of finasteride have been seen (see section 4.2)

Finasteride has been found to cross the blood-barrier. Small amounts have been recovered in the seminal fluid of treated. In 2 studies of healthy subjects (n=69) receiving finasteride 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/ml) to 10.54 ng/ml. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving finasteride 5 mg/day ranged from undetectable (<1.0 ng/ml) to 21 ng/ml. Thus, based on a 5-ml ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 μ g) that had no effect on circulating DHT levels in men.(see also section 5.3.).

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.

5.3 PRECLINICAL SAFETY DATA

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

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman would be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1 million times the estimated amount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose."

6 PHARMACEUTICAL PARTICULARS**6.1 LIST OF EXCIPIENTS**

Tablet Core

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

Film coating

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; 7, 12, 14, 28, 30, 49, 50, 56, 98, 100 and 300 tablets
2. Al/Al Blister, pack sizes; 7, 12, 14, 28, 30, 49, 50, 56, 98, 100 and 300 tablets

Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

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

7 MARKETING AUTHORISATION HOLDER

Hikma Limited,
13 Hanover Square,
London W15 1HW,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 29412/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/03/2008

10 DATE OF REVISION OF THE TEXT

04/03/2008

PATIENT INFORMATION LEAFLET

Finasteride 5 mg tablets

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 any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Finasteride tablets are and what they are used for
2. Before you take Finasteride tablets
3. Special precautions
4. How to take Finasteride tablets
5. Possible side effects
6. How to store Finasteride tablets
7. Further information

1. What Finasteride is and what it is used for
Finasteride belongs to a group of medicines called 5-alpha reductase inhibitors. They act by reducing the size of the prostate gland in men.

Finasteride is used in the treatment and control of benign (not cancerous) enlargement of the prostate.

2. Before you take Finasteride tablets

- Do not take Finasteride tablets if you
- are allergic (hypersensitive) to finasteride or any of the other ingredients in Finasteride tablets (see section 7)
 - are a woman

Check with your doctor or pharmacist before taking Finasteride tablets if you

- have reduced liver function
- have difficulty emptying your bladder completely or a greatly reduced flow of urine.

Your doctor should examine you before you start taking Finasteride tablets to exclude other obstructions in the urinary tract.

Taking other medicines

Finasteride tablets can normally be taken with other medicines. However, please ask your doctor or pharmacist before you take other medicines at the same time or if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

3. Special precautions

Finasteride tablets are only intended for men.

Pregnancy

Women who are pregnant or may become pregnant should not handle broken or crushed Finasteride tablets. If finasteride is absorbed through the skin or taken by mouth by a woman pregnant with a male foetus, the child may be born with malformed genital organs. The tablets are film-coated, which prevents contact with finasteride provided the tablets are not broken or crushed.

If your sexual partner is or may possibly be pregnant, you must avoid exposing her to your semen, which could contain a small amount of the drug. If you think a pregnant woman has come into contact with finasteride, you should consult a doctor.

Driving and using machines

There is no evidence to suggest that Finasteride tablets affect the ability to drive or use machines.

Sugar intolerance

Finasteride tablets contain lactose monohydrate. If you do not tolerate some types of sugar, contact your doctor before you take this medicine.

Blood tests

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

4. How to take Finasteride tablets

Always take Finasteride tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

The usual dose is 1 tablet daily.

The tablet should be swallowed whole and should not be broken or crushed. It may be taken with or without food.

If you stop taking Finasteride tablets

Although an improvement is often noticed after a short time, it may be necessary to continue the treatment for at least 6 months. **Do not alter the dose or stop treatment without asking your doctor.**

If you take more Finasteride tablets than you should

If you (or someone else) swallow a lot of the tablets at the same time, or you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

If you forget to take Finasteride tablets

Do not take a double dose to make up for a forgotten tablet. Just take the next one when it is due.

5. Possible side effects

Like all medicines, Finasteride tablets can cause side effects, although not everybody gets them.

Stop taking Finasteride tablets and contact your doctor immediately if you develop any of the following symptoms: swelling of the face, tongue or lips, difficulty swallowing or urticaria (itchy skin rash) and difficulty breathing.

Please tell your doctor or pharmacist if you notice any of the following effects or any side effects not listed:

Very Common (*occur in more than 1 in 10 users*)
Inability to obtain an erection

Common (*occur in more than 1 in 100 users*)
Reduced sex drive, difficulty ejaculating, reduced amount of ejaculatory fluid, tenderness and/or enlargement of the breasts, rash.

Less common (*occur in less than 1 in 100 users*)
Testicular pain

Rare (*occur in less than 1 in 1000 users*)
Itching and skin redness, difficulty sleeping.

Very rare (*occur in less than 1 in 10,000 users*)

Leaking of fluid from the male breasts, occasionally a lump which may need to be surgically removed from the male breast.

6. How to store Finasteride tablets

Keep out of the reach and sight of children.

There are no special storage precautions.

Use before the expiry date which is stated on the package. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. Further information**What Finasteride tablets contain**

- The active substance (the ingredient which makes the medicine work) is finasteride 5 mg
- The other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, lauroyl macroglycerides, sodium starch glycolate (type A), magnesium stearate. The film coating contains hypromellose, macrogol 6000, titanium dioxide (E171) and indigocarmine lake (E132).

What Finasteride tablets look like and contents of the pack

The tablets are blue, round, biconvex film-coated tablets with a diameter of 7 mm, marked 'F5' on one side.

They are supplied in:

Blister packs containing 7, 14, 28, 30, 49, 50, 56, 98, 100 or 300 tablets.

Not all pack sizes may be available.

Marketing Authorisation Holder

Hikma Limited
13 Hanover Square
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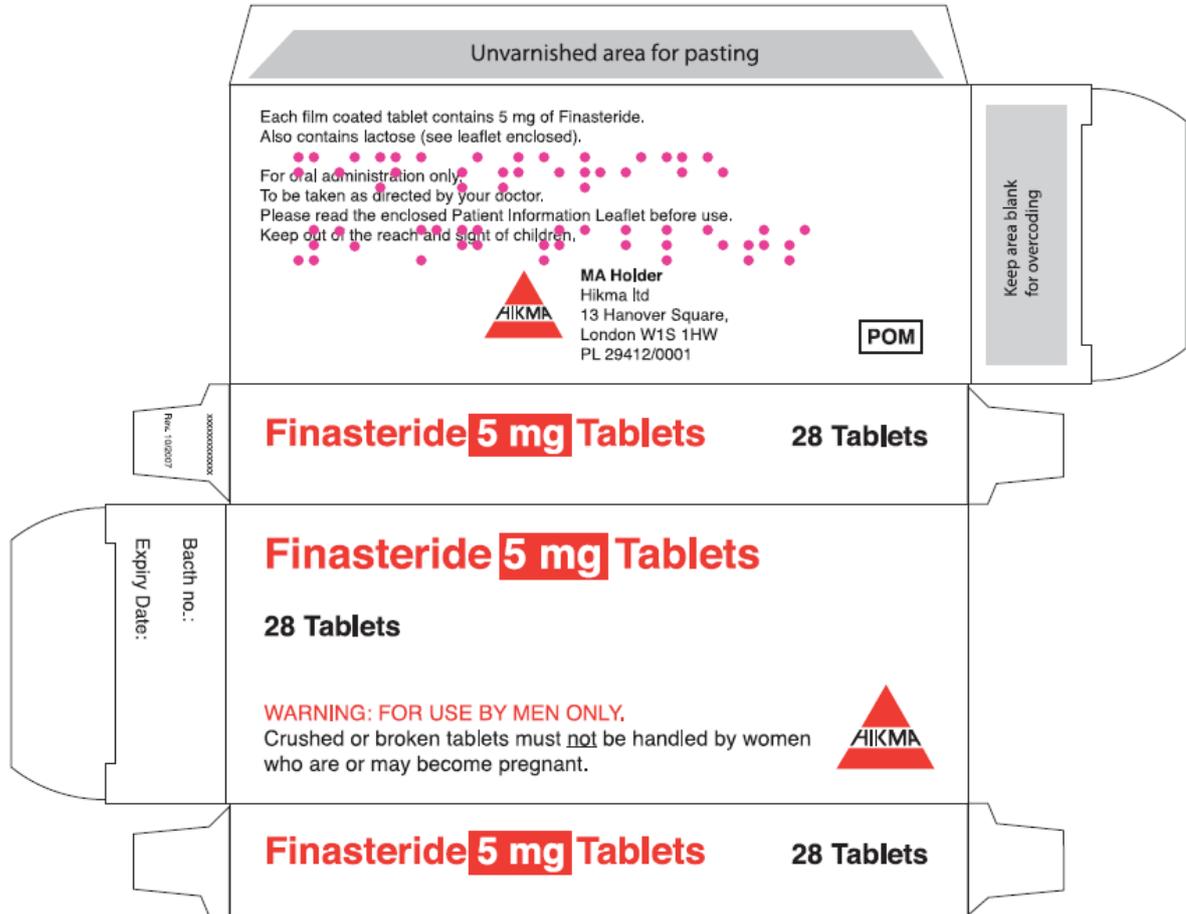
Manufacturer

Actavis Group hf
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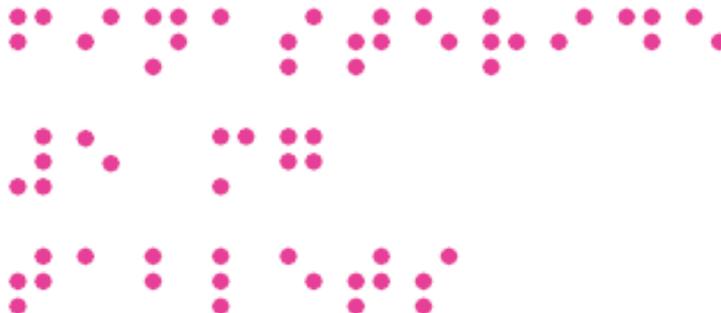
This leaflet was last approved in November 2007

LABELLING

Carton for blisters, with braille. Pack size 28.



Braille



Blister foil

