FINASTERIDE 5MG TABLETS (FINASTERIDE)

PL 06464/2430

UKPAR

TABLE OF CONTENTS

FINASTERIDE 5MG TABLETS (FINASTERIDE)

PL 06464/2430

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Waymade plc a Marketing Authorisation (licence) for the medicinal product Finasteride 5mg Tablets (PL 06464/2430) on 20th November 2007. 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 product of the reference product Proscar 5mg 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 this application and it was therefore judged that the benefits of taking Finasteride 5mg Tablets outweigh the risk, hence a Marketing Authorisation has been granted.

FINASTERIDE 5MG TABLETS (FINASTERIDE)

PL 06464/2430

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Waymade plc a Marketing Authorisation for the medicinal product Finasteride 5mg Tablets (PL 06464/2430) on 20th November 2007. 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 5α-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.

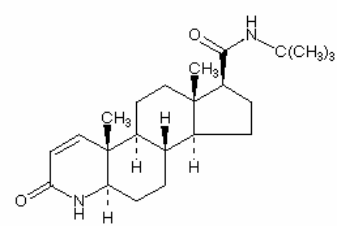
The application depends upon the bioequivalence study presented by the applicant comparing the test product Finasteride 5mg Tablets with the reference product Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited).

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Finasteride

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



Molecular formula: $C_{23}H_{36}N_2O_2$
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 Ph. Eur. 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.

Active finasteride is stored in appropriate packaging. It is packed in virgin food grade double transparent polythene bags. The bags 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.

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

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±2°C/60±5%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, hypromellose, colloidal anhydrous silica, 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 Pharmacopoeial 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 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 products, 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 has been carried out on validation batches. 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

Three types of primary packaging are proposed for the marketed product:
(1) PVC/aluminium blister - pack sizes 12, 28, 30 and 56
(2) Aluminium/aluminium blister - pack sizes 12, 28, 30 and 56
(3) HDPE containers with a tamper evident screw cap closure made of LDPE - pack sizes 50, 75 and 100

The MAH have stated that not all pack sizes will be marketed. Additionally, the HDPE containers are not currently being 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).

Product Information
The approved SPC, 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. A more detailed evaluation of the bioequivalence study is found in the clinical assessment.

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 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 in patients with BPH. The indications are consistent with those for the innovator product.

POSOLOGY 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 06464/2430, Waymade plc), to the reference product Proscar 5mg Tablets (PL 00025/0279; Merck Sharp and Dohme Limited). 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). 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 %**
$AUC_{0\text{-}inf}$ ng*h/ml	304	299	97.4 to 106
$AUC_{0\text{-}t}$ 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 Cmax, 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
The final SmPC is consistent with that for the innovator product, as well as with SPCs harmonized through Europe, and it is acceptable.

Patient Information Leaflet
The approved PIL is in line with the SPC, consistent with that of the innovator product 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 SPC, 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.

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 active substance. The risk: benefit is, therefore, considered to be positive.

FINASTERIDE 5MG TABLETS (FINASTERIDE)

PL 06464/2430

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 7th November 2006

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 9th February 2007

3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 22nd February 2007

4 The applicant responded to the MHRA's request, providing further information for the quality sections on 11th April 2007

5 Following assessment of the response the MHRA requested further information relating to the quality sections on 11th April 2007

6 The applicant responded to the MHRA's request, providing further information for the quality sections on 10th May 2007

7 Following assessment of the response the MHRA requested further information relating to the quality sections on 30th May 2007 and further information relating to the clinical sections on 6th September 2007

8 The applicant responded to the MHRA's requests, providing further information for the quality sections and clinical sections on 19th November 2007

9 The application was determined on 20th November 2007

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 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. Blue, round biconvex 7 mm film-coated tablet 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 within a short time, treatment for at least six months may be necessary in order to determine objectively whether a satisfactory response to the treatment has been achieved.
Dosage in Children: Finasteride is contraindicated 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 adjustments are not necessary in patients with varying degrees of renal insufficiency (starting from creatinine clearance as low as 9 ml/min) as in pharmacokinetic studies renal insufficiency was not found to affect the elimination of Finasteride. Finasteride has not been studied in patients on haemodialysis.

4.3 CONTRAINDICATIONS

Hypersensitivity to finasteride or to any of the excipients.

Contraindicated in women who are or may potentially become pregnant (see sections 4.4, 4.6 and 6.6).

Finasteride is not indicated in 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.
- Consultation of an urologist should be considered in patients treated with finasteride.
- Ostruction 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 metabolised 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 intolerance, 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 thenormal 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 or specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to finasteride therapy. Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride 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 foetus. Finasteride tablets have a film coating which prevents contact with the active ingredient provided that the tablets have not been broken or crushed (see section 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 P450linked 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, betablockers, calcium channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMGCoA reductase inhibitors, nonsteroidal antiinflammatory 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 contraindicated during pregnancy. Because of the ability of Type II 5 α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, might 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 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 foetus (see section 6.6). Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Finasteride has a film coating 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. When the patient's sexual partner is or may potentially be pregnant, the patient is recommended to minimise exposure of his partner to semen. *Lactation*: Finasteride 5 mg film-coated 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 a transient nature on continued treatment.

Reproductive System and breast disorders

Very Common (> 1/10):

- Impotence

Common (> 1/1000, < 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 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 a greater frequency in patients receiving the combination (see table below).

System organ class	Placebo N=737 ***N=737***	Doxazosin N=756 ***N=756***	Finasteride N=768 ***N=768***	Finasteride + Doxazosin 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
Asthenia	7.1	15.7	5.3	16.8
Cardiac disorders	10.4	23.1	12.6	22.0
Hypotension° Orthostatic hypotension	0.7 8.0	3.4 16.7	1.2 9.1	1.5 17.8
Nervous system disorders	16.1	28.4	19.7	36.3
Dizziness Reduced libido Somnolence	8.1 5.7 1.5	17.7 7.0 3.7	7.4 10.0 1.7	23.2 11.6 3.1
Uro-genital disorders	18.6	22.1	29.7	36.8
Ejaculation disorders Breast enlargement Impotency Other sexual abnormalities	2.3 0.7 12.2 0.9	4.5 1.1 14.4 2.0	7.2 2.2 18.5 2.5	14.1 1.5 22.6 3.1

Laboratory test findings: Serum PSA concentration is correlated with patient group 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 details and clinical interpretation 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, a specifc competitive inhibitor of the intracellular enzyme Type-II-5a-reductase. The enzyme converts testosterone into the more potent androgen dihydrotestosterone (DHT). The prostate gland and, consequently, also the hyperplasic prostate tissue are dependent on the conversion of testosterone to DHT for their normal function and growth. Finasteride has no affinity for the androgen receptor.

Clinical studies show a rapid reduction of the serum DHT levels of 70%, which leads to a reduction on prostate volume. After 3 months, a reduction of approx. 20% in the volume of the gland occurs, and the shrinking continues and reaches 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 four and seven months, respectively.

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

Effect 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 within 68 hours.

Distribution:

Binding to plasma proteins is approx. 93%.

Clearance and volume of distribution are approx. 165 ml/min (70-279 ml/min) and 76 l (44-96 l), respectively. Accumulation of small amounts of finasteride is seen on repeated administration. After a daily dose of 5 mg the lowest steady-state concentration of finasteride has been calculated to be 8-1 0 ng/ml, which remains stable over time.

Biotransformation:

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

Elimination:

The plasma half-life averages 6 hours (4-12 hours) (in men >70 years of age, 8 hours, range 6-15 hours). After administration of radioactively labelled finasteride, approx. 39% (32-46%) of

the given dose is excreted in the urine in the form of metabolites. Virtually no unchanged finasteride is recovered in the urine. Approximately 57% (51-64%) of the total dose is excreted in the faeces. In patients with impaired renal function (creatinine clearance as low as 9 ml/min), no changes in the elimination of finasteride have been seen (See section 4.2).

Finasteride has been found to cross the bloodbrain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients. 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 μg) 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 955 ml/min, the disposition of a single dose of 14Cfinasteride 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 nondialysed 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 could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1 million times the estimated mount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose."

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core

Lactose monohydrate

Cellulose microcrystalline

Pregelatinised starch

Lauroyl macrogoglycerides

Sodium starch glycolate (Type A)

Magnesium stearate

Film coating

Hypromellose 6 cps.

Titanium dioxide (E171)

Indigo carmine lake (E132)

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

7 MARKETING AUTHORISATION HOLDER
Waymade PLC
Trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex.
SS14 3FR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 06464/2430

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/11/2007

10 DATE OF REVISION OF THE TEXT
20/11/2007

PATIENT INFORMATION LEAFLET

797-7952
Patient Information Leaflet

SOVEREIGN MEDICAL

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

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
- are a child as finasteride tablets are not recommended for children.

Check with your doctor or pharmacist before taking Finasteride Tablets if you
- 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
- have liver problems.

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

Breast feeding

This medicinal product is only intended for men. It is not known if finasteride is excreted in breast milk.

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 potentially be pregnant, you should avoid exposing her to your semen, which could contain a tiny 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.
The most frequent side effects are impotence (inability to obtain an erection) and decreased sex drive. These effects usually occur at the beginning of the treatment and in most patients they are short-term.
Other side effects that may occur have been listed by body systems and frequency.

The frequencies are defined as:
Very common (occur in more than 1 in 10 patients), common (occur in less than 1 in 10 but more than 1 in 100 patients), uncommon (occur in less than 1 in 100 but more than 1 in 1,000 patients), rare (occur in less than 1 in 1,000 but more than 1 in 10,000 patients), very rare (occur in less than 1 in 10,000 patients, including isolated reports).

Skin disorders
Uncommon: Skin rash
Rare: Pruritus (itching), urticaria (hives)

Reproductive system and breast disorders
Very common: Impotence (inability to obtain an erection)
Common: Reduced libido (decreased sex drive), reduced volume of ejaculate
Uncommon: Breast tenderness/breast enlargement, ejaculation disorder
Rare: Testicular pain
Very rare: Breast secretion, breast nodules that were surgically removed in a few patients

General disorders
Rare: Hypersensitivity (allergic) reactions such as swelling of the face and lips

Stop taking this product and contact your doctor immediately if you develop any of the following symptoms: swelling of the face, tongue or lips, difficulty swallowing or urticaria and difficulty breathing.

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. If possible note what you experienced and when it started and how long it lasted.

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

What Finasteride Tablets look like and contents of the pack

The tablets are film-coated, blue, round, biconvex.
They are supplied in:
Blister packs containing 12, 28 or 30 or 56 tablets.
Plastic bottles containing 50, 75 or 100 tablets.

Not all pack sizes may be available.

Marketing Authorisation Holder

Waymade PLC, trading as Sovereign Medical, Sovereign House, Miles Gray Road, Basildon, Essex. SS14 3FR.

The Manufacturer Responsible for Release is:

Waymade PLC, Sovereign House, Miles Gray Road, Basildon, Essex. SS14 3FR.

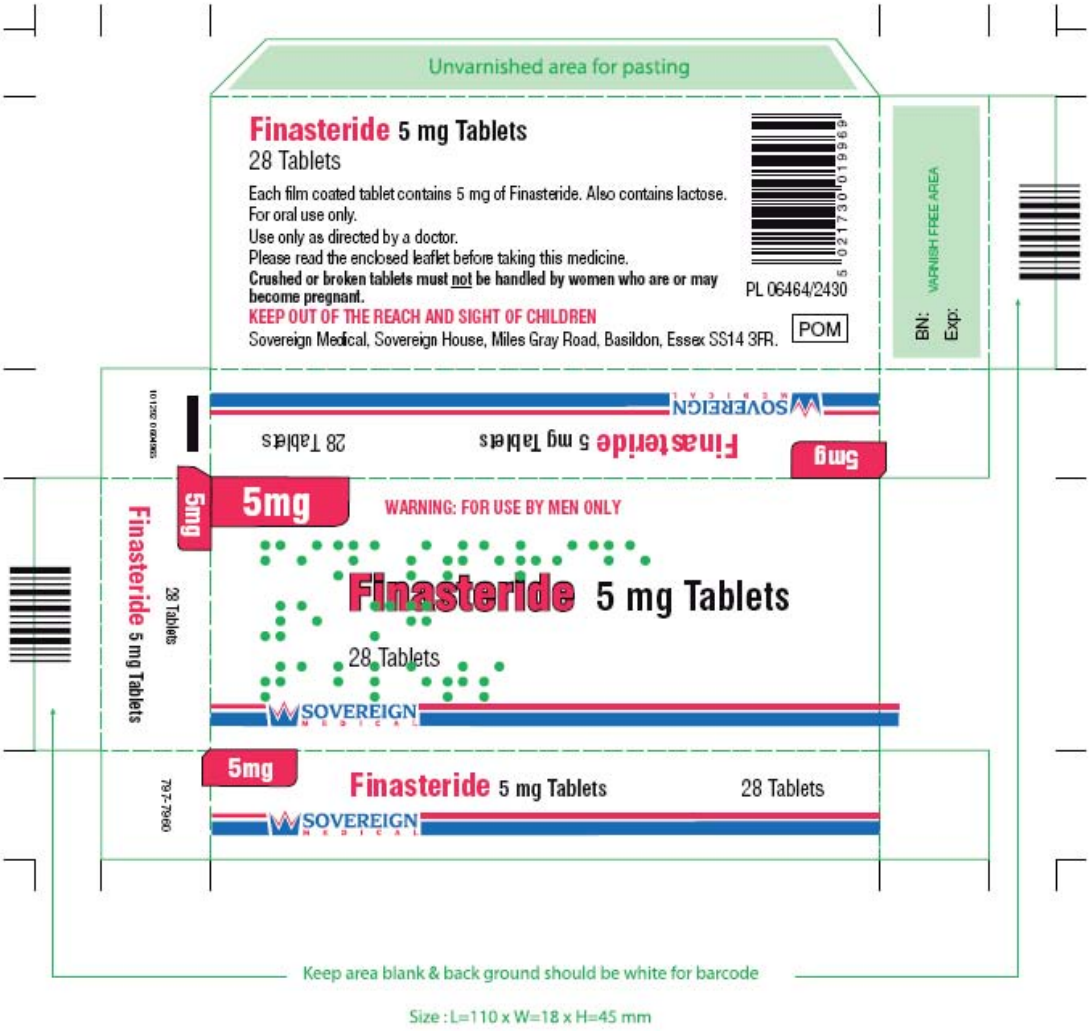
This leaflet was last approved in October 2007

10 1294 0 604966

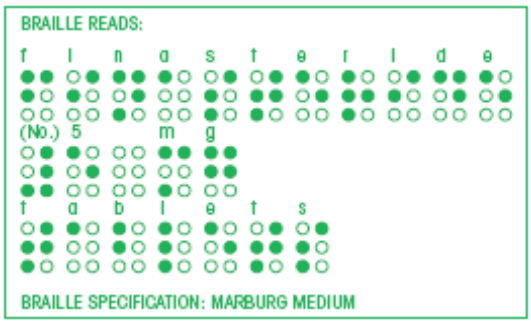
SOVEREIGN MEDICAL

LABELLING

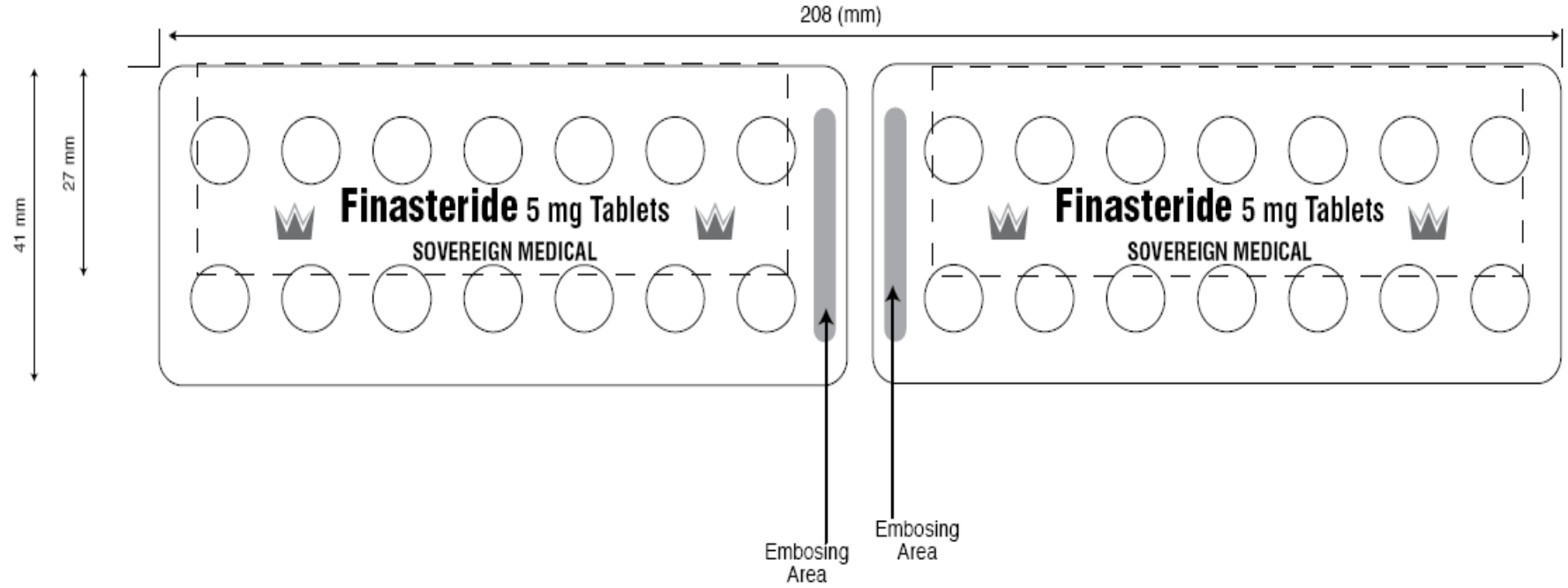
Pack size 28



Braille



Blister


208 (mm)
41 mm
27 mm
Finasteride 5 mg Tablets
SOVEREIGN MEDICAL
Finasteride 5 mg Tablets
SOVEREIGN MEDICAL
Embosing Area
Embosing Area