FINASTERIDE 5 MG TABLETS
PL 08137/0147

UKPAR

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FINASTERIDE 5 MG TABLETS
PL 08137/0147

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency (MHRA) granted Neolab Limited a Marketing Authorisation (licence) for the medicinal product Finasteride 5mg Tablets (PL 08137/0147). This medicine is available on 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 this application and it was therefore judged that the benefits of taking Finasteride 5 mg Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
FINASTERIDE 5 MG TABLETS  
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Finasteride 5mg Tablets (PL 08137/0147) on 30th April 2009. The product is a prescription-only medicine.

This is a national application for Finasteride 5mg film-coated Tablets submitted under Article 10.1 of Directive 2001/83/EC, as amended, which has been shown to be a generic medicinal product of the original, Proscar 5 mg Tablets (PL 00025/0279) authorised to Merck, Sharp and Dohme Ltd in May 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.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**

**Finasteride**

INN: Finasteride  
Chemical Name:  
1. \( N-(1,1\text{-Dimethylethyl})-3\text{-oxo-4-aza-5α-androst-1-ene-17b-carboxamide} \) (Ph Eur name) 
2. \( N\text{-tert-Butyl-3-oxo-4-aza-5α-androst-1-ene-17 β-carboxamide} \) 
3. \( (5α-17β)-N-(1,1\text{-Dimethylethyl})-3\text{-oxo-4-azaandrost-1-ene-17- carboxamide} \) 
4. \( 17β-(N\text{-tert-butylcarbomyl})-4\text{-aza-5α-androst-1-en-3-one} \)

Structure:

![Structure of Finasteride](image)

Molecular formula: \( \text{C}_{23}\text{H}_{36}\text{N}_{2}\text{O}_{2} \)  
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

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

An appropriate specification based on the European 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.

A suitable retest period has been determined based on the stability data submitted.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely lactose monohydrate, sodium starch glycolate (Type A), maize starch, colloidal anhydrous silica, docusate sodium, sodium benzoate, magnesium stearate. All ingredients within the tablet core comply with relevant Ph Eur monographs.

The tablet coating consists of: hypromellose, titanium dioxide (E171), macrogol and indigo carmine (E132). The ingredients within the tablet coating comply with in-house specifications. Appropriate justification for the inclusion of each excipient has been provided. Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contain 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 those intended for human consumption.

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 production-scale 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 blister strips composed of opaque polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) with aluminium lids. Specifications and certificates of analysis for the 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 28 tablets.

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
The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

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 5 mg Tablets are indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:

- cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH.

- reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

POSOLOGY AND METHOD OF ADMINISTRATION

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

Finasteride 5 mg Tablets 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 5 mg Tablets are contra-indicated in children.

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
To confirm essential similarity with the UK and European brand leader, Proscar® Tablets, comparative data, including impurity and dissolution profiles are presented for UK supplied Proscar® Tablets.

Comparative Bioequivalence Study against the UK Brand Leader

The objective of the study was to compare the bioavailability of the test product one 5mg finasteride tablet, with one 5mg Proscar tablet manufactured by Merck Sharp and Dohme Limited, Hoddesdon, UK, administered under fasting conditions. The reference product is acceptable as it is marketed in the UK.

Satisfactory Certificates of Analysis for the test and reference products are provided. Satisfactory comparative dissolution profiles are provided for the test and reference products.

Twenty eight healthy male volunteers were included in a two-period, two-treatment, single dose, randomised two-sequence crossover bioequivalence study. Venous blood samples were collected pre-dose and up to 36 hours post dose. The two treatment periods were separated by a washout period of 8 days (accepted as the elimination half-life of finasteride is approximately 7 hours).

Plasma concentrations of finasteride were determined using a validated method.

The pharmacokinetic parameters (tmax, Cmax, AUCo-t and AUCo-α) were determined for the test and reference drugs. The two formulations were compared by ANOVA applied to log transformed data. Data from the first 24 subjects who completed the study were used for pharmacokinetic analysis. Although all 28 volunteers completed the study, sample analysis was performed on samples from 24 subjects only in accordance with the study protocol. The results are given below in Table 1. There were no adverse events noted in the study.
Table 1: Pharmacokinetic parameters of finasteride in bioequivalence study

<table>
<thead>
<tr>
<th>PHARMACOKINETIC PARAMETERS OF FINASTERIDE (N=24)</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Cmax (ng/ml)*</td>
</tr>
<tr>
<td>AUC 0-t (ng.h/ml)*</td>
</tr>
<tr>
<td>AUC 0-∞(ng.h/ml)*</td>
</tr>
<tr>
<td>tmax (h)**</td>
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<td>t½ (h) **</td>
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</tbody>
</table>

* Geometric mean data
**Mean value

Based on data from 24 subjects, the bioavailability parameters (AUCo-α, AUCo-t and Cmax) were within the 90% CI limit of 80-125%. Therefore, the two products are considered bioequivalent, in line with NfG CPMP/EWP/QWP/1401/98 “The Investigation of Bioavailability and Bioequivalence

Assessor Comment:
Bioequivalence has been proven between the test product, 5mg Finasteride Tablets and the innovator product, Proscar 5mg Tablets marketed by Merck Sharp and Dohme Limited.

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.

LABELLING
This is satisfactory.

APPLICATION FORM
This conformed to EC requirements and was satisfactory.

DISCUSSION
This is a National application 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
A product licence 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 an application 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.
## STEPS TAKEN FOR ASSESSMENT

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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 22nd November 2006.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 1st February 2007.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 27th February 2009.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 25th March 2009 for the clinical sections.</td>
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<tr>
<td>5</td>
<td>The applications were determined on 30th April 2009.</td>
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FINASTERIDE 5 MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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1 NAME OF THE MEDICINAL PRODUCT
Finasteride 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains Finasteride 5 mg.

Excipient:
Lactose monohydrate: 91.450 mg (per tablet).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet. Light blue, circular.

Finasteride 5 mg Tablets are light blue, circular biconvex film-coated tablets, ‘FNS 5’ debossed on one side, plain on the other.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Finasteride 5 mg Tablets are indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate to:

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The recommended adult dose is one 5 mg tablet daily, with or without food.

Finasteride 5 mg Tablets 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 5 mg Tablets are contra-indicated in children.

4.3 CONTRAINDICATIONS
Hypersensitivity to any component of this product; women who are or may potentially be pregnant; children
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

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

Effects on prostate-specific antigen (PSA) and prostate cancer detection

No clinical benefit has yet been demonstrated in patients with prostate cancer treated with Finasteride 5 mg Tablets.

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 5 mg Tablets 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 5 mg Tablets. A baseline PSA <4 ng/ml does not exclude prostate cancer.

Finasteride 5 mg Tablets cause 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 5 mg Tablets 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 5 mg Tablets 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 5 mg Tablets.

Percent free PSA (free to total PSA ratio) is not significantly decreased by Finasteride 5 mg Tablets and remains constant even under the influence of Finasteride 5 mg Tablets. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No clinically important drug interactions have been identified. Finasteride 5 mg Tablets do not appear to significantly affect the cytochrome P450 linked drug metabolising enzyme system. Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed in clinical studies, Finasteride 5 mg Tablets 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 5 mg Tablets is contra indicated in women who are or may potentially be pregnant.

Because of the ability of Type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male 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 5α-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 5α-reductase. It is for these reasons that Finasteride 5 mg Tablets 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 5 mg Tablets 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 5 mg 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 Tablets once daily. 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 5 mg Tablets.

Lactation: Finasteride 5 mg Tablets is not indicated for use in women. It is not known whether finasteride is excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None reported.

4.8 UNDESIRABLE EFFECTS

Finasteride 5 mg Tablets are 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 5 mg Tablets 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 whom 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving Finasteride and 1147 (24.4%) men receiving placebo. In the ‘finasteride’ group, 280 (6.4%) 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 tumours 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 5 mg Tablets. 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 5 mg Tablets 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 5 mg Tablets in standard laboratory tests.

4.9 OVERDOSE

No specific treatment of overdosage with Finasteride 5 mg Tablets is recommended. Patients have received single doses of up to 400 mg and multiple doses of up to 80 mg/day for up to three months without any adverse effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: G04C B01

Finasteride is a competitive inhibitor of human Type II 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 5 mg Tablets are 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 5 mg Tablets 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
Medical therapy of prostatic symptoms

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day *, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥ 4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34 (p=0.002), 39 (p<0.001), and 67% (p<0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥ 4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67 (p=0.011), 31 (p=0.296), and 79% (p<0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.

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

5.2 PHARMACOKINETIC PROPERTIES

After an oral dose of 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 5α-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
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential. Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated 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
- Sodium starch glycolate (Type A)
- Maize starch
- Colloidal anhydrous silica
- Docusate sodium
- Sodium benzoate
- Magnesium stearate

Tablet coat:
- Hypromellose
- Titanium dioxide (E171)
- Macrogol
- Indigo carmine (E132)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
Three years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters strips comprising opaque PVC/PVdC film and Aluminium lid enclosed in an outer carton.

Pack sizes of 28 tablets.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Women should not handle crushed or broken Finasteride 5 mg 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
Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)
PL 08137/0147

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30/04/2009

10 DATE OF REVISION OF THE TEXT
30/04/2009
FINASTERIDE 5 MG TABLETS
PL 08137/0147
PATIENT INFORMATION LEAFLET

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

Finasteride Tablets are used for the treatment of a condition called benign prostatic hyperplasia (BPH) which is common in older men. BPH is caused by the prostate gland growing too big and obstructing the flow of urine from the bladder. This leads to some unpleasant symptoms such as weak or interrupted urine flow, a need to pass water more frequently and/or a sudden need to pass water.

Finasteride Tablets work by helping to shrink the enlarged prostate and relieve your symptoms. It will help reduce the risk of you developing a sudden inability to pass urine (known as acute urinary retention) and the need for surgery.

2. BEFORE YOU TAKE FINASTERIDE TABLETS

Do not take Finasteride Tablets if:
- you are allergic (hypersensitive) to finasteride, any other 5-alpha reductase inhibitor or any of the other ingredients in the tablets (these are listed in section 6).

Further information:
- female Finasteride Tablets are for use by men only.
- you are a male under 16 years of age.
- if any of the above apply to you, talk to your doctor who will decide what to do.

Take special care with Finasteride Tablets

Pregnancy and breast-feeding women

Women who are pregnant, likely to become pregnant or breast-feeding must not be exposed to Finasteride. They must not take Finasteride Tablets or handle broken or unused tablets. Also if your sexual partner may potentially be pregnant, you must avoid exposing her to your semen which must contain a small amount of finasteride which could affect the normal development of a male baby. This can be done by using a condom during sexual activity. Talk to your doctor who will help decide what you should do.

If a pregnant woman comes into contact with the active ingredient in Finasteride Tablets (for example by handling broken tablets or by ingesting it), please contact a doctor immediately.

3. HOW TO TAKE FINASTERIDE TABLETS

Swallow.

Take Finasteride Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The tablet on the container will tell you when to take the tablet.

The usual dose for Finasteride Tablets is as follows:

Adults and elderly: take one tablet daily with or without food.

In order to treat your symptoms and control your BPH effectively, it is important that you continue to take Finasteride Tablets as long as your doctor prescribes. Even if you do not feel an immediate benefit.

Some patients show early improvement in symptoms, but you may need to take Finasteride Tablets for at least 6 to 12 months to see if it improves your symptoms. Finasteride Tablets work best when taken long term.

Your doctor may prescribe Finasteride Tablets along with another medicine called dutasteride to help you control your BPH.

Finasteride Tablets are not suitable for use by children.

Method of Administration

Each tablet should be swallowed whole with plenty of water with or without food. Take your tablet at the same time each day.

If you take more Finasteride Tablets than you should:

If you or someone else takes more than the prescribed dose, contact your doctor or pharmacist immediately. However, it is unlikely to take place even remaining tablets you intend to use for Finasteride Tablets.

Do not worry. Simply leave that dose completely and take your next dose at the right time. Do not take a double dose or make up for a missed dose.

4. POSSIBLE SIDE EFFECTS

Side effects: Finasteride Tablets can cause side effects, although not everybody

Allergic reactions:

All medicines can cause allergic reactions although sensitive reactions are rare. If you get any of the following symptoms when taking these tablets, you should stop taking these tablets and contact your doctor immediately.

- Any skin reaction, difficulty in breathing or tightening, swelling of the face, lips, mouth or throat;
- Swelling of the legs;
- Feeling faint or dizzy;
- Trouble breathing;
- Numbness or tingling in the skin, mouth, eyes and genitalia;
- Uneasiness in your whole body.

The following side effects have also been reported:

- Weakness and tiredness (occasionally affecting less than 1 in 100 men)
- Headache (occasionally affecting less than 1 in 100 men)
- Rash (occasionally affecting less than 1 in 100 men)
- Changes or problems with ejaculation such as a decrease in the amount of semen ejaculated.

Uncommon side effects:

The following side effects are rare:

- Skin rash;
- Difficulty in passing urine.

If any of these side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FINASTERIDE TABLETS

This medicinal product does not require any special storage conditions. Do not use it after the expiry date which is shown on the pack after EXP. Keep Finasteride Tablets out of reach of children.

Medicines should not be disposed of via waste water or household waste. If you have any Finasteride Tablets after completing your course of treatment, please return them to your pharmacist who will dispose of them safely.

These measures will help protect the environment.

6. FURTHER INFORMATION

What Finasteride Tablets contain:

Each tablet contains 5 mg of Finasteride. Finasteride Tablets contain the following active ingredients:

- Finasteride;
- Talc;
- Carboxymethylcellulose sodium;
- Acacia;
- Magnesium Stearate;
- Hydroxypropylmethylcellulose (HPMC);
- Magnesium Stearate.

What Finasteride Tablets look like and the contents of the pack:

Finasteride Tablets are light blue, round-shaped tablets, manufactured with a DPH 9 on one side and a plain circle on the other.

Your medicine is available in bottles containing 20 tablets.

Marketing Authorisation Holder and Manufacturer:

The Marketing Authorisation holder for this medicine is: Europharm Limited, 51 High Street, Chislehurst, Kent, BR7 5JX.

This leaflet was last updated on ...
FINASTERIDE 5 MG TABLETS
PL 08137/0147

LABELS

Finasteride 5 mg
Film-coated Tablets

Each tablet contains Finasteride 5 mg.

For oral use.
Take as directed by your doctor.
Please read the enclosed leaflet carefully before use.
Also contains lactose.
Crushed or broken tablets must not be handled by women who are or may become pregnant.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Finasteride 5 mg
Film-coated Tablets

WARNING: FOR USE BY MEN ONLY

28 Film-coated Tablets

Blister foil