Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Finasteride 5 mg film-coated tablets

Finasteride

PL 21300/0012

UK/H/1059/01/MR

MPX International Limited

Medicines and Healthcare products Regulatory Agency

Lay Summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted MPX International Limited a Marketing Authorisation (licence) for the medicinal product Finasteride 5 mg film-coated tablets (Product Licence number: 21300/0012).

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.

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

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Module 1

Information about initial procedure

Name of the product in the Reference Member State	Finasteride 5 mg film-coated tablets
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 Generic, Article 10.1 Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Finasteride
Pharmacotherapeutic classification	5α-reductase inhibitor
Pharmaceutical form and strength(s)	Film-coated tablet, 5mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1059/01/MR
Reference Member State	United Kingdom
Member States concerned	Sweden
Date of first authorisation	9 November 2006
Marketing Authorisation Number(s)	PL 21300/0012
Name and address of the authorisation holder	MPX International Limited, 127 Shirland Road, London, W9 2EP, UK

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5.0 mg finasteride.

Excipients: Each film-coated tablet contains 102.63 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

White or almost white, rounded triangle shaped, slightly biconvex film-coated tablets, with an imprinted mark "RG" on one side.

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.

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

4.2 Posology and method of administration

The recommended adult dose is one 5 mg tablet daily, with or without food.
Finasteride tablets are taken orally.
The tablet must be swallowed whole and must not be divided or crushed (see section 6.6).
Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1 'Pharmacodynamic properties').
The recommended duration of treatment is a minimum of six months to achieve clinical efficacy, but finasteride may also be continued at unchanged doses (as maintenance therapy).
Even if improvement can be seen within 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

No dosage adjustment is needed in patients with varying degrees of renal insufficiency (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.
Dosage adjustments are not necessary although pharmacokinetic studies have shown that the elimination rate of Finasteride is slightly decreased in patients above 70 years of age.
There are no data available in patients with hepatic insufficiency (see section 4.4).
Finasteride is contraindicated in adolescents and children under the age of 18 years.

4.3 Contraindications

Hypersensitivity to finasteride or to any of the excipients of the preparation.
Women, who are or may potentially be pregnant, and children should not take Finasteride.

4.4 Special warnings and precautions for use

- Finasteride is intended exclusively for men.
  Consultation with a urologist should be considered in patients treated with finasteride
  Before starting finasteride therapy, any other condition which may cause difficulties in passing urine (such as prostatic carcinoma, stricture of the urethra, neurological disorders) should be excluded.
  Since improvement of the condition cannot be achieved immediately, patients with high residual volume or severely decreased urinary flow rate should be carefully monitored for obstructive uropathy.
- There is no experience in patients with hepatic insufficiency. Caution is advised in patients with impaired hepatic function as the plasma levels of Finasteride may be increased in such patients.
- 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, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with finasteride and periodically thereafter. Generally, when PSA assays are performed a baseline PSA>10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with finasteride. A baseline PSA <4 ng/ml does not exclude prostate cancer.
  Finasteride causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with finasteride should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with finasteride for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.
  Any sustained increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to therapy with

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

- Pregnant women and women of childbearing potential, specifically those who intend to get pregnant and those, in whom pregnancy cannot be excluded, should not touch broken or crushed tablets and should avoid contact with the seminal fluid of treated men throughout the treatment period and for two months after termination of the treatment. Finasteride is classified as a pregnancy category X compound.
- It is recommended to perform laboratory tests, liver and kidney function tests, blood count and urinary sediment tests before starting finasteride therapy and every six months during treatment. Namely, a large amount of finasteride is metabolised in the liver.
- In case of lactose intolerance it should be taken into account that the Finasteride 5 mg tablets contain 102.63 mg lactose as well.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically important drug interactions have been identified. Finasteride does not appear to significantly affect the cytochrome P450 linked drug metabolising enzyme system.

Compounds which have been tested in man include propranolol, digoxin, glibenclamide, warfarin, theophylline, and antipyrine and no clinically meaningful interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed in clinical studies, finasteride was used concomitantly with ACE inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H_2 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.

Drug-lab modifications

Finasteride decreases the prostate-specific antigen (PSA) values in the serum.

4.6 Pregnancy and lactation

Pregnancy:

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

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

In animal developmental studies, dose-dependent development of hypospadias were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 µg/kg/day to 100 mg/kg/day, at an incidence of 3.6% to 100%. Additionally, pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, transient nipple development and decreased anogenital distance, when given finasteride at doses below the recommended human dose. The critical period during which these effects can be induced has been defined in rats as days 16-17 of gestation.

The changes described above are expected pharmacological effects of Type II 5 α-reductase inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed *in utero* to finasteride are similar to those reported in male infants with a genetic deficiency of Type II 5 α-reductase. It is for these reasons that finasteride is contra-indicated in women who are or may potentially be pregnant.
No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Exposure to finasteride risk to male foetus:
Women should not handle crushed or broken tablets of finasteride when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see 'Pregnancy'). Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Small amounts of finasteride have been recovered from the semen in subjects receiving finasteride 5 mg/day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. Therefore, when the patient's sexual partner is or may potentially be pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue finasteride.

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

4.7 Effects on ability to drive and use machines

Finasteride does not influence the ability to drive and use machines.

4.8 Undesirable effects

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

Reproductive system and breast disorders
Common (>1/100, 1<10):
Impotence, reduced libido, reduced volume of ejaculate
Uncommon (>1/1000, 1<100):
Breast tenderness/breast enlargement, ejaculation disorder
Rare (>1/10000, 1<1000):
Testicular pain
Very rare (>1/100000), including isolated reports:
Breast secretion, breast nodules that were surgically removed in single patients

Skin and subcutaneous tissue disorders
Uncommon (>1/1000, 1<100):
Skin rash
Rare (>1/10000, 1<1000):
Pruritus, urticaria

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%.

Other long-term data
In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 9,060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving finasteride and 1,147 (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.

Laboratory test findings
When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with finasteride. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with finasteride for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men.
For clinical interpretation see 'Special warnings and precautions for use', *Effects on prostate-specific antigen (PSA) and prostate cancer detection.*
No other difference was observed in patients treated with placebo or finasteride in standard laboratory tests.

4.9 Overdose
No side effects were observed in patients given a single dose of up to 400 mg finasteride or in patients experimentally treated with 80 mg finasteride daily for 3 months. Thus, there are no recommendations as to treatment of overdosage owing to lack of experience up to now.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: G04C B01
Pharmacotherapeutic group: Testosterone-5α-reductase inhibitor

Finasteride is a competitive inhibitor of human 5 α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. Finasteride

is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

Clinical studies show a rapid reduction of the serum DHT levels of 70%, which leads to a reduction of 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 couple of weeks, compared with the start of treatment. Differences from placebo have been documentated 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.

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

Absorption
The bioavailability of finasteride is approx. 80%. Peak plasma concentrations are reached approx. 2 hours after intake, and absorption is complete after 6-8 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 8-10 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 5α-reductase-inhibiting effects have been identified.

Elimination:
The plasma half life is a mean of 6 hours (4-12 hours) (in men > 70 years: 8 hours, range 6 –15 hours). Following administration of radioactively labelled finasteride, approx. 39% (32 – 46%) of the dose was excreted in the urine in the form of metabolites. Virtually no unchanged Finasteride was recovered in the urine. Approx. 57% (51 – 64%) of the total dose was excreted in the faeces.
In patients with renal impairment (creatinine clearance above 9 ml/min), no changes in the elimination of finasteride have been seen (see section 4.2).

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

5.3 Preclinical safety data
No further information provided.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:
Magnesium stearate
Talc
Sodium starch glycolate (type A)
Pregelatinised starch
Microcrystalline cellulose
Lactose monohydrate

Tablet coating:
Titanium dioxide (C.I.77891, E171)
Lactose monohydrate
Macrogol 6000
Hyprolose
Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister packs of hard aluminium foil and white, hard PVC foil containing 7x, 10x, 14x, 15x, 28x, 30x, 50x, 56x, 90x, 98x, 100x, 105x, 120x tablets.
(Not all pack sizes may be marketed.)

6.6 Special precautions for disposal and other handling

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 4.6).

7 MARKETING AUTHORISATION HOLDER

MPX International Limited
127 Shirland Road
W9 2EP London
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 21300/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2006

10 DATE OF REVISION OF THE TEXT

08/02/2008

Module 3

Product Information Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

FINASTERIDE 5 MG FILM-COATED TABLETS

Active substance: 5 mg finasteride in each tablet.

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, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it onto 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 5 MG FILM-COATED TABLET IS AND WHAT IT IS USED FOR

Your doctor has prescribed Finasteride 5 mg film-coated tablets because you have a condition known as benign prostatic hyperplasia or BPH.

Your prostate, a gland located near your urinary bladder that produces a fluid in which the spermatozoids are transported, has become bigger and is making it more difficult for you to pass urine.

Finasteride reduces the size of the enlarged prostate and relieves urinary symptoms, such as the need to urinate frequently especially at night, painful urination, weak urine stream, sensation that the urinary bladder is not completely empty. Finasteride reduces the need for surgery.

2. BEFORE YOU TAKE FINASTERIDE 5 MG FILM-COATED TABLETS

Do not take Finasteride 5 mg film-coated tablets:

- If you are **allergic (hypersensitive)** to finasteride or any of the other ingredients.
- **Women and children** should not take finasteride. The condition for which finasteride is prescribed occurs only in men.

Take special care with Finasteride:

- Tell your doctor about any medical problems you have or have had, and about any allergies.

- Finasteride 5 mg film-coated tablets are for use in men only in the treatment of BPH. Women who are or may potentially be pregnant must not use finasteride, nor should they handle crushed or broken tablets of finasteride. If the active ingredient in Finasteride 5 mg film-coated tablets is absorbed after oral use or through the skin by a woman who is pregnant with a male foetus, then it is not known whether the development of the external male organs in the foetus may be adversely affected. If your sexual partner is or may be pregnant then avoid exposing her to your semen (during and for two months after treatment ends) which could contain a small amount of finasteride- e.g. by using a condom during sexual activity. **If a woman who is pregnant comes into contact with the active ingredient in the tablet, a doctor should be consulted.** Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. If you have any doubts, ask your doctor.

- BPH develops over a long period of time. Sometimes symptoms improve promptly, but you may need to take finasteride for at least six months to see if it improves your symptoms. Whether or not you notice any improvement or change in symptoms, therapy with finasteride may reduce the risk of inability to pass urine and, therefore, the need for surgery. **You must visit your doctor regularly for periodic checkups and an evaluation of your progress.** While BPH is not cancer and does not lead to cancer, the two conditions can exist at the same time. Only a doctor can evaluate your symptoms and their possible causes.

- Finasteride can reduce the prostate-specific antigen levels (PSA, a body substance which increases when the prostate grows and can cause obstruction). If you have a PSA test done, tell your doctor that you are taking finasteride.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Taking finasteride with food and drink:
Take one tablet of finasteride every day, with or without food.

Pregnancy, breast-feeding:
Ask your doctor or pharmacist for advice before taking any medicine.
Finasteride is for use in men only.
Finasteride is not indicated for use in women or children.

Driving and using machines:
Finasteride should not affect your ability to drive or operate machinery.

Important information about some of the ingredients of Finasteride 5 mg film-coated tablets:
In patients with **lactose intolerance** it should be taken into account that the Finasteride 5 mg film-coated tablet contains 102.63 mg lactose as well.
If your attention was drawn to **intolerance of certain kinds of sugar** by your doctor, you should see your doctor before you take this medicine.

3. HOW TO TAKE FINASTERIDE 5 MG FILM-COATED TABLETS

Always take Finasteride 5 mg film-coated tablets exactly as your doctor has told you. You should check with your doctor if you are not sure.

Do not change the doses or stop taking it without consulting your doctor before.

Take one tablet of finasteride every day, with or without food. Finasteride is administered orally.
Follow these instructions unless your doctor gave you different advice, otherwise finasteride may not produce the desired effect. Remember to take your medicine.

The improvement of the symptoms might be visible at once, though sometimes you may need to take finasteride for at least six months to see improvement.

If you TAKE MORE finasteride than you should:
In case of overdose or accidental ingestion, advise your doctor immediately.

If you FORGET TO TAKE finasteride:
If you miss a dose, do not take an extra one. Just take the next tablet as usual.
Do not take a double dose to make up for a forgotten dose.

If you STOP TAKING finasteride:
You should not stop taking it without consulting your doctor before.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Finasteride 5 mg film-coated tablets can cause side effects, although not everybody gets them.

The most frequently observed side effects are: impotence (an inability to have an erection), decreased sex drive, decreased amount of semen released during sex (this does not appear to interfere with normal sexual function), ejaculation disorders, breast enlargement, rash, breast tenderness, that develops in less than 10% but more than 1% of patients.

The following additional adverse experiences have been reported in post-marketing experience: testicular pain, itching, urticaria, swelling of lips and face.

In some cases, these side effects disappeared while the patient continued to take finasteride.
If symptoms persisted, they usually resolved on discontinuing finasteride treatment.

If any of the following happen, stop taking finasteride and tell your doctor immediately or go to the casualty department at your nearest hospital:
- swelling of the hands, feet, ankles, face, lips, mouth, or throat which may cause difficulty in swallowing or breathing
- urticaria (hives)
- fainting.

If you have any of these side effects, you may be having an allergic reaction to finasteride. You should see a doctor immediately, so the doctor can assess how serious these side effects are.
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.

5. HOW TO STORE FINASTERIDE 5 MG FILM-COATED TABLETS

Store in the original package in order to protect from light.

Keep out of the reach and sight of children.

Do not use Finasteride 5 mg film-coated tablets after the expiry date which is stated on the carton and blisters after mm.yyyy (abbreviation used for expiry date). The expiry date refers to the last day of that month.
Leave your tablets in the foil. Only remove them when it is time to take your medicine.

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.

6. FURTHER INFORMATION

What Finasteride 5 mg film-coated tablet contains

The active substance is: 5 mg of finasteride in each tablet.
The other ingredients are:
Tablet core: magnesium stearate, talc, sodium starch glycolate (type A), pregelatinised starch, microcrystalline cellulose, lactose monohydrate.
Tablet coating: titanium dioxide (C.I.77891, E171), lactose monohydrate, macrogol 6000, hyprolose, hypromellose.

What Finasteride 5 mg film-coated tablet looks like and contents of the pack

White or almost white, rounded triangle shaped, slightly biconvex film-coated tablets, with an imprinted mark "RG" on one side.
Blister packs of hard aluminium foil and white, hard PVC foil containing 7x, 10x, 14x, 15x, 28x, 30x, 50x, 56x, 90x, 98x, 100x, 105x, 120x tablets. (Not all pack sizes may be marketed.)

Marketing Authorisation Holder and Manufacturer

For any information about this medicinal product, please contact the Marketing Authorisation Holder.

Marketing Authorisation Holder:
MPX International Limited
127 Shirland Road
W9 2EP London
United Kingdom

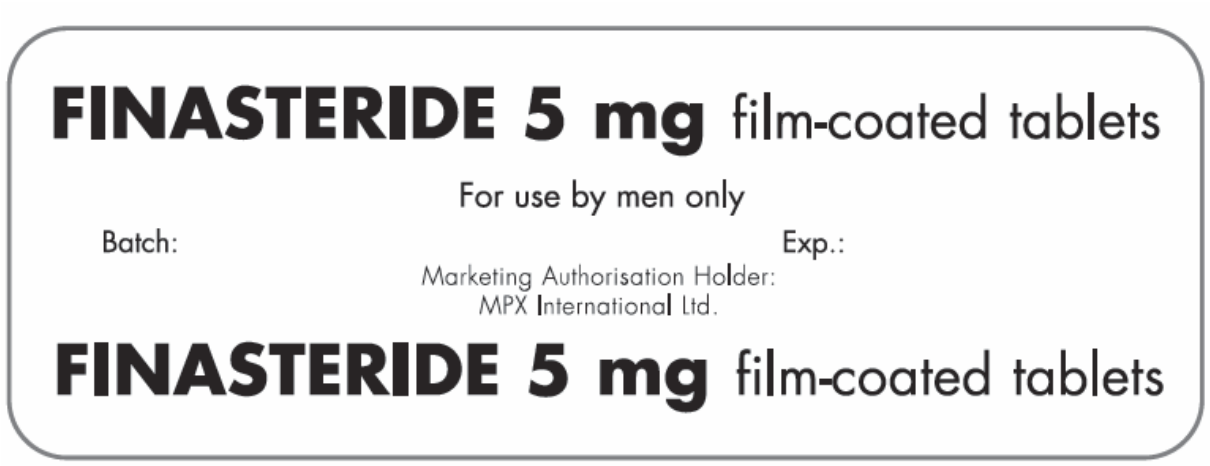
Manufacturer:
Gedeon Richter Ltd.,
X. Gyömrői út 19-21.
Budapest, Hungary

This leaflet was last approved in 10/2006.

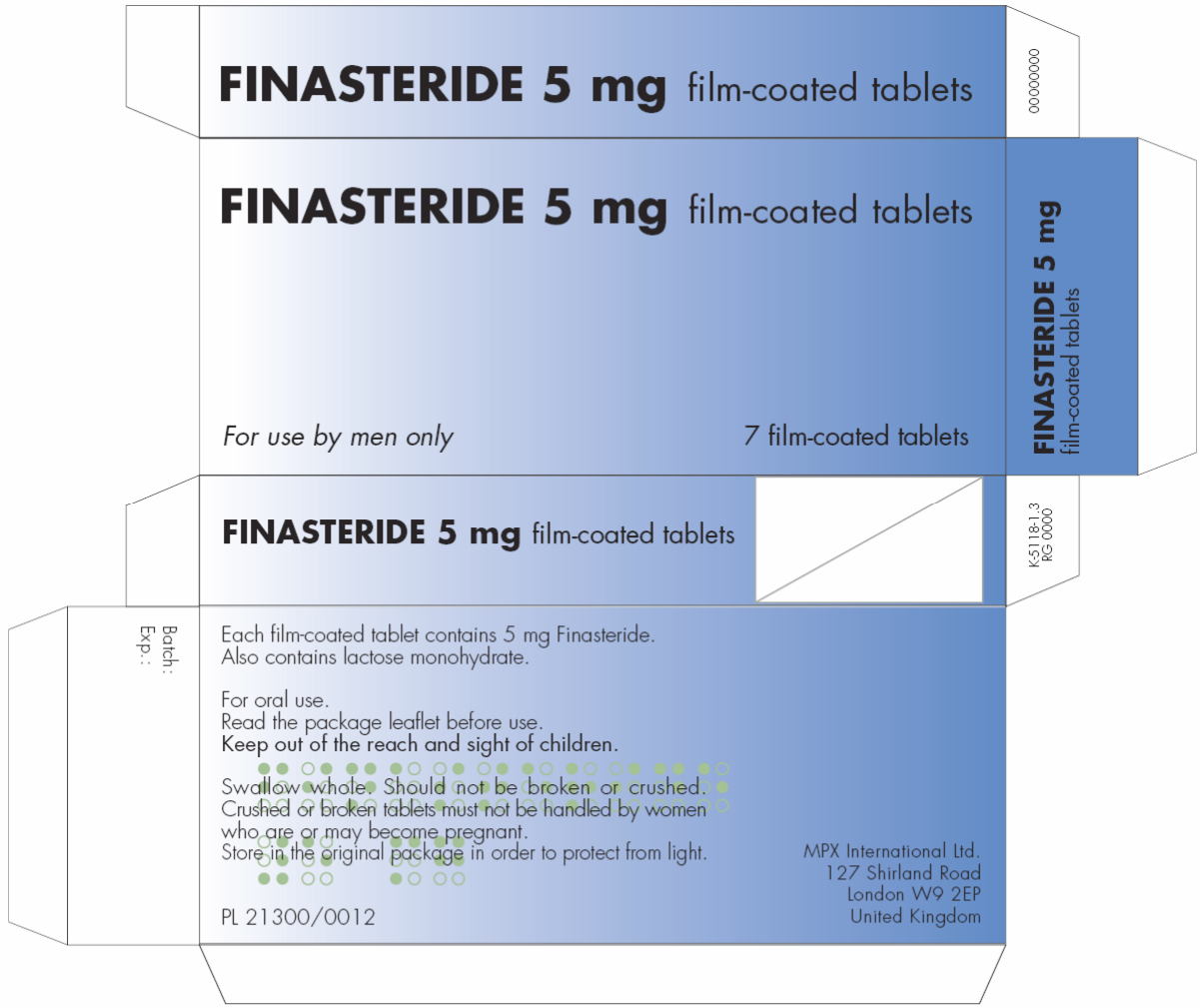
Module 4

Labelling

Blister:



Carton:


FINASTERIDE 5 mg film-coated tablets
00000000
FINASTERIDE 5 mg film-coated tablets
FINASTERIDE 5 mg
film-coated tablets
For use by men only
7 film-coated tablets
FINASTERIDE 5 mg film-coated tablets
K-5118-1.3
RG 0000
Batch:
Exp.:
Each film-coated tablet contains 5 mg Finasteride.
Also contains lactose monohydrate.
For oral use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Swallow whole. Should not be broken or crushed.
Crushed or broken tablets must not be handled by women who are or may become pregnant.
Store in the original package in order to protect from light.
PL 21300/0012
MPX International Ltd.
127 Shirland Road
London W9 2EP
United Kingdom

Module 5

Scientific discussion during initial procedure

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Finasteride 5 mg film-coated tablets in the treatment and control of benign prostatic hyperplasia, could be approved. A national marketing authorisation was granted on 9 November 2006.

II EXECUTIVE SUMMARY

II.1 Problem statement

This mutual recognition application considers a generic version of Finasteride 5mg film-coated tablets.

The UK application for this product was submitted under Article 10.1 of Directive 2001/83/EC (as amended) as a so called generic application. A marketing authorisation for Finasteride 5mg film-coated tablets was granted in the UK on 9 November 2006. With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, MPX International Limited, is applying for a Marketing Authorisation for Finasteride 5mg film-coated tablets in Sweden (UK/H/1059/001/MR).

The original product is listed as Proscar 5mg tablets, licensed in April 1992 to Merck, Sharp and Dohme in Austria. The reference product is Proscar 5mg tablets licensed to Merck, Sharp and Dohme in May 1992 (PL 00025/0279). The medicinal product used in the bioequivalence study was Proscar 5mg tablets sourced from UK.

II.2 About the product

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

II.3 The development programme

The aim of the development programme was to develop a tablet containing active finasteride that is suitably stable and bioequivalent to the originator product, Proscar 5mg Tablets (Marketing Authorisation Holder: Merck, Sharp and Dohme Limited, UK).

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

No clinical efficacy studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

III SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The specification for finasteride is in line with the specifications in the European Pharmacopoiea monograph. All batches of active substance are tested to the full specification by the finished product manufacturer. Satisfactory batch analysis data have been provided for active substance manufactured by the active substance manufacturer.

Satisfactory stability data have been provided for the active substance to support a retest period of 6 months when stored in well-closed packaging and protected from light.

Drug product

The aim of the development programme was to develop a tablet containing finasteride as active that is suitably stable and is bioequivalent to the originator product, Proscar 5mg Tablets (Marketing Authorisation Holder: Merck, Sharp and Dohme Limited, UK). Results from bioequivalence studies have been submitted, showing that this product (Finasteride 5mg film-coated tablets) and the reference product (Proscar 5mg Tablets) are essentially similar.

All excipients are standard pharmaceutical ingredients and comply with the requirements of the relevant European Pharmacopoeia monographs. Relevant TSE certificates have been provided for lactose monohydrate. No other excipients contain materials of animal or human origin. The finished product is packed in to blisters of white hard PVC foil and aluminium foil. Pack sizes are 7, 10, 14, 15, 28, 30, 50, 56, 90, 98, 100, 105 and 120 tablets per pack.

The proposed finished product specification is appropriate for a product of this type and is controlled with valid methods. Stability studies on the product have been conducted under ICH conditions and support a shelf life of 24 months with the storage condition “Store in original package to protect from light”. This is acceptable.

The PIL user testing has been assessed by the RMS. 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.

Non-clinical aspects

The applicant's expert provides a sufficiently comprehensive overview of the pharmacology and toxicology of finasteride. No new preclinical toxicology data were submitted, which is acceptable given the nature of the application.

Clinical aspects

The applicant has undertaken bioequivalence studies that compare the pharmacokinetic parameters of its formulation to that of the reference product, Proscar. Although results for the 90% confidence interval for AUC_{0-t} and C_{max} for the initial study do not fall within the predefined limits to demonstrate bioequivalence, it appears that this is due to the outlying results of subject number 6, in whom plasma levels of the reference product (Proscar 5 mg) were very low (virtually undetectable) compared to plasma levels of the test product. There is no clinical or other explanation for this discrepancy, however, given that discrepancy lies within the results for the reference product and that plasma levels were virtually zero it seems acceptable to exclude the results for this patient from the analysis. When a subsequent appropriate re-analysis was undertaken, the results for the 90% confidence interval for AUC_{0-t} and C_{max} fall within the predefined limits and bioequivalence is demonstrated.

The applicant has submitted the results from two other bioequivalence studies which are supportive of the bioequivalence of this product to Proscar 5 mg, albeit to reference product obtained in the USA. When considering the nature of the discrepancy in the original bioequivalence study and the subsequent re-analysis of the results, and the additional supportive data, it can be considered that essential similarity has been demonstrated according to the requirements of the CPMP NfG on the investigation of bioavailability and bioequivalence.

The SPC, PIL and packaging comply with current guidelines and are consistent with those of the reference product.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

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.

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

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

Appropriate stability data have been generated supporting the retest period of 6 months when stored in well-closed packaging and protected from light

DRUG PRODUCT

The tablets are coated, white or almost white, rounded triangle, 7mm in height with the marking '$^{R}_{G}$' on one side.

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely magnesium stearate, talc, sodium starch glycolate (type A), pregelatinised starch, microcrystalline cellulose and lactose monohydrate, which comprise the tablet core, and titanium dioxide (C.I.77891, E171), lactose monohydrate, macrogol 6000, hyprolose and hypromellose, which comprise the tablet coating.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

Manufacture

A 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 batches of each strength. 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 finished product is packed into blisters of white hard PVC foil and aluminium foil.

Acceptable specifications and certificates of analysis have been provided from the finished product manufacturer. Relevant certification on compliance with the EU directives for contact materials has been provided for the PVC and aluminium foils.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. The storage condition is "Store in the original package in order to protect from light."

Bioequivalence
The bioequivalence study was performed at a suitable site. This was a single centre, open label, randomised, two way cross-over, single dose study performed under fasting conditions comparing the Finasteride 5mg tablets with Proscar 5mg tablets from Merck, Sharp and Dohme Limited (sourced from the UK) in healthy adult males, at a dose of 5mg. Twenty six subjects were enrolled in the study. Data were analysed for twenty four, due to one withdrawal and one drop-out.

One 5 mg tablet was given for each of the medications. Samples were taken predose (0 hours) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16 and 24 hours post dose. The washout period was 7 days.

Bioequivalence was determined using the 90% confidence interval of the relative mean C_{max} and AUC_{0-t} (primary target parameters) of the test to reference formulation, which should be 80 to 125%. AUC_{∞}, T_{max}, Kel, elimination half-life and residual area were used as secondary parameters.

Bioequivalence was demonstrated.

Essential similarity
The dissolution profiles of the biobatch of Finasteride 5mg tablets have been shown to be comparable to Proscar 5mg tablets. This included the batch of Proscar 5mg tablets used in the bioequivalence study. Individual tablet data have been presented. All products show comparability.

Comparative impurity profiles have been demonstrated for Finasteride 5mg tablets and Proscar 5mg tablets.

PRODUCT LITERATURE
All product literature is satisfactory.

CONCLUSIONS AND ADVICE
A marketing authorisation can be granted.

NON-CLINICAL ASSESSMENT

These applications are made under Article 10.1 of Directive 2001/83/EC and refer to the original products Proscar 5mg Film-Coated Tablets (Marketing Authorisation Holder: Merck, Sharp and Dohme, Austria). These original products have been licensed in at least one EEA member state for over 10 years. No new preclinical data have been supplied with this application and none are required.

CLINICAL ASSESSMENT

1. INTRODUCTION

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

This application is presented as an essentially similar product to Proscar 5mg tablets (PL 00025/0279), manufactured by Merck Sharpe and Dohme Limited.

2. BACKGROUND

Merck Sharpe and Dohme Limited was granted a product licence (00025/0279) in the UK for their Proscar 5 mg tablets on 4 April 2002. Proscar 5mg tablets were first licensed in the EEA in France in 1992, the applicant has supplied proof of this; thus the 10 year rule has been fulfilled.

3. INDICATIONS

The applicant has submitted the following:

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. DOSE & DOSE SCHEDULE

The recommended adult dose is one 5 mg tablet daily, with or without food.
Finasteride tablets are taken orally. The tablet must be swallowed whole and should not be crushed or broken. Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1 'Pharmacodynamic properties').

The recommended duration of treatment is a minimum of six months to achieve clinical efficacy, but finasteride may also be continued at unchanged doses (as maintenance therapy).

No dosage adjustment is needed in patients with renal insufficiency (creatinine clearance as low as 9 ml/min) or in patients over 70 years of age. There are no data available in patients with hepatic insufficiency.
Finasteride is contraindicated in adolescents and children under the age of 18 years.

5. TOXICOLOGY

No formal data is provided under this heading and none are required for this application.

6. CLINICAL PHARMACOLOGY

A bioequivalence study comparing one 5 mg finasteride film coated tablet to one 5 mg Proscar tablet was undertaken. The study was a randomised, single-dose, cross-over study that was carried out in 24 healthy male volunteers. The volunteers, after fasting overnight, received either one 5 mg Finasteride 5 mg film coated tablet or one 5 mg Proscar Tablet, after a washout period of 7 days they received the alternative therapy. Blood samples were taken for measuring plasma levels of finasteride pre-dose and at regular intervals up to 24 hours post-dose.

Statistical analysis of the pharmacokinetic parameters was undertaken according to the study protocol using analysis of variance on the results of the first 24 patients who completed the study. Point estimates and 90% confidence intervals for the "test/reference" mean ratios of those variables were calculated.

The results for the 90% confidence interval for AUC_{0-t} and C_{max} do not fall within the predefined limits. It appears that this is due to the outlying results of subject number six, in whom plasma levels of the reference product (Proscar 5 mg) were very low compared to plasma levels of the reference product. No reason for the low concentration values of subject number six could be found by the CRO for the trial and it has been suggested that the dissolution of the affected tablet could have been inadequate. When the data for this subject are treated as that of a statistical outlier and a non-parametric analysis is undertaken the results for ratio of the 90% confidence intervals AUC_{0-t} and C_{max} are 90.31% to 102.79% (mean= 96.7%) and 91.3% to 103.48% (mean 96.87%) respectively. Bioequivalence is, therefore, demonstrated.

In addition, data from two bioequivalence studies performed in the USA were provided. These data do seem to provide evidence of bioequivalence.

7. EFFICACY

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

8. SAFETY

No formal safety data are presented. The adverse events that can be expected are listed in the SPC and are consistent with those for the reference product.

9. CLINICAL OVERVIEW

There is a clinical overview from a consultant to the pharmaceutical industry who is appropriately qualified.

10. SUMMARY OF PRODUCT CHARACTERISTICS

This is consistent with the SPC for Proscar 5 mg tablets and is satisfactory.

11. PATIENT INFORMATION LEAFLET

The patient information leaflet is satisfactory.

12. LABELLING

All labelling is satisfactory.

13. MAA

The MAA is satisfactory.

14. DISCUSSION

The information submitted with this application is satisfactory.

15. CONCLUSIONS

This application is satisfactory and a product licence may be granted.

OVERALL CONCLUSION

QUALITY

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

PRECLINICAL

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

EFFICACY

The efficacy of finasteride has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with Finasteride 5mg film-coated tablets. The risk benefit is therefore considered to be positive.

Module 6

Steps take after initial procedure

A national, type II variation was granted on 18 October 2007 to add the warnings 'For use by men only' and 'Crushed or broken tablets must not be handled by women who are or may become pregnant' blister foil and carton, respectively.