Public Assessment Report

Decentralised Procedure

Finasteride 5 mg Film-coated Tablets

PL 28309/0001

UK/H/931/001/DC

esparma GmbH
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted esparma GmbH a Marketing Authorisation (licence) for the medicinal product Finasteride 5 mg Film-coated Tablets (Product Licence number: 28309/0001). This medicine is available on prescription only.

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

The data submitted in support of this application for Finasteride 5 mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweighs the risks; hence a Marketing Authorisation has been granted.
TABLE OF CONTENTS

Module 1: Information about decentralised procedure Page 4
Module 2: Summary of Product Characteristics Page 5
Module 3: Product Information Leaflets Page 14
Module 4: Labelling Page 19
Module 5: Scientific Discussion Page 25

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions
# Module 1

## Information about decentralised procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Finasteride 5 mg Film-coated Tablets</th>
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<td></td>
<td>39171 Osterweddingen</td>
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<td></td>
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Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Finasteride 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One film-coated tablet contains 5 mg finasteride.
For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Film-coated tablet
White, round, biconvex, film-coated tablets marked ”F” on the one side and ”5” on the other. Diameter 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Finasteride 5 mg Film-coated Tablets is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with enlarged prostate to:
- cause regressions 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
For oral use only.
The recommended dose is 5 mg daily given as a single dose. The tablets should be swallowed whole and should not be broken or crushed (see section 6.6). Although early improvement can be seen, treatment for at least six months may be necessary to assess whether a beneficial response to treatment has been achieved.
Finasteride 5 mg Film-coated Tablets can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1 ‘Pharmacodynamic properties’)
Treatment with Finasteride 5 mg Film-coated Tablets should occur in consultation with an urologist or surgeon specialising in urological surgery.

Hepatic- or renal impairment
The effects of liver impairment on the pharmacokinetics of finasteride have not been studied, therefore caution should be observed in patients with moderate to severely impaired liver function.
No adjustment of dose is considered necessary in patients with renal impairment (see section 5.2).
Dosage in the elderly
No adjustment of dose is necessary even though pharmacokinetic studies have demonstrated that the elimination rate for finasteride is somewhat slower in patients over 70 years (see section 5.2).

4.3 Contraindications
Finasteride 5 mg Film-coated Tablets is contraindicated for use by women and children (see section 4.6 and 5.3). Hypersensitivity towards finasteride or to any of its excipients.

4.4 Special warnings and precautions for use
Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy. Surgical intervention should be considered for these patients.

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

No clinical benefit has yet been demonstrated in patients with prostate cancer treated with finasteride.
Digital rectal examination, and, if necessary, determination of prostate-specific-antigen (PSA) in serum should be carried out on patients prior to initiating therapy with finasteride and periodically during treatment to rule out prostate cancer. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with finasteride.
Finasteride causes a decrease in serum PSA concentrations by approximately 50% in patients with BPH even in the presence of prostate cancer. This decrease in serum PSA levels in patients with BPH treated with finasteride should be considered when evaluating PSA data and does not rule out concomitant prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. In patients treated with finasteride for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity or specificity of the PSA assay and maintains its ability to detect prostate cancer.
Any sustained increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance to finasteride therapy.
Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride and remains constant even under the influence of finasteride. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment is necessary.
One tablet of this drug contains 75.00 mg lactose monohydrate. Patients with the following rare hereditary condition should not use this medicinal product: galactose intolerance, total absence of lactase, or glucose-galactose malabsorption.
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, H2 antagonists, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation
Pregnancy:
Finasteride is contraindicated in women who are or may potentially be pregnant.
As with other 5-alpha-reductase inhibitors, finasteride inhibits the conversion of testosterone to dihydrotestosterone and may inhibit development of the external genitalia of a male foetus when administered to a pregnant woman (see section 5.3). Women should not handle crushed or broken tablets when they are or may potentially be pregnant, due to the potential for absorption of finasteride and the subsequent potential risk to a male foetus. Finasteride 5 mg Film-coated 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.

In animal developmental studies, dose-dependent hypospadias were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 µg/kg/day to 100mg/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 alpha-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 alpha-reductase.
It is for these reasons that Finasteride 5 mg Film-coated Tablets is contraindicated in women who are or may potentially be pregnant.

Similarly small amounts of finasteride have been recovered from the semen in subjects receiving Finasteride 5 mg Film-coated Tablets 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.

No effects were seen in female offspring exposed in utero to any dose of finasteride.

Lactation:
Finasterid 5 mg Film-coated 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
There are no data which suggest that Finasteride 5 mg Film-coated Tablets affects the ability to drive or use machines.

4.8 Undesirable effects
The most commonly occurring adverse reactions are impotence and diminished libido (6-8%; placebo 3-4%). These reactions are more common during the first year than in the following year of treatment

Common (>1/100)
General: Impotence.
Other: Decreased libido, decreased volume of ejaculate, ejaculation disorder, breast tenderness/breast enlargement, skin rash.

Less common (1/100- 1/1000)
General: Skin rash.

Rare (<1/1000)
General: Hypersensitivity reactions including swelling of the face and lips.
Skin: Pruritus, urticaria.
Other: Testicular pain.

There was no evidence of increased adverse experiences with increased duration of treatment with finasteride and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.

Laboratory tests:
When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with finasteride. In a majority of the patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with finasteride for six months or more, PSA values should be doubled for comparison to normal ranges in
untreated men. For details and clinical interpretation see section 4.4 (paragraph Effects on prostate-specific antigen (PSA) and prostate cancer detection).
No other difference was observed in patients treated with placebo or finasteride in standard laboratory tests.

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%.

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%) of men receiving finasteride and in 1147 (24.4%) of 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 versus 237 (5.1%) in the placebo group. 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.

4.9 Overdose
Single doses of up to 400 mg finasteride and multiple doses of up to 80 mg/day for three months (n=71) have not resulted in dose related side effects.
No specific treatment of overdose with Finasteride esparma is recommended.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological group: Agent used in benign prostatic hyperplasia, testosterone-5-a-reductase inhibitor
ATC-code: G04CB01
Finasteride is a 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme, type 2 5-a-reductase. The enzyme converts testosterone to the more potent androgen dihydrotestosterone (DHT). The prostate gland, and consequently also hyperplastic prostate tissue are dependent on the conversion of testosterone to DHT for their normal function and growth. Finasteride has no affinity for the androgen receptor. Clinical studies show a rapid reduction in DHT-levels in serum by 70%, which leads to a reduction in the prostate volume. After 3 months, a reduction in gland size by approximately 20% occurred. The shrinkage continues to reach 27% after 3 years. The most pronounced reduction takes place in the
periurethral zone, which directly surrounds the urethra. Urodynamic measurements have also confirmed a significant reduction in detrusor pressure as a result of the reduced obstruction. Significant improvements in maximum urinary flow rate and symptoms occur as early as two weeks after the start of treatment. Differences from placebo were recorded at respectively 4 and 7 months. All effective parameters were upheld during three years of follow up. The effects on symptoms and maximum urinary flow correlate positively to the size of the prostate when the treatment is commenced.

**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

**Bioavailability:**
The bioavailability is approximately 80% and is unaffected by food. Maximum plasma concentrations are reached after approximately 2 hours and absorption is complete within 6-8 hours.

**Distribution:**
Protein binding is approximately 93%. The volume of distribution is approximately 76 litres (44-96 L). At steady state, following a daily dose of 1 mg, the mean maximum plasma concentration of finasteride was 9.2 ng/ml and was achieved 1-2 hours after dosing. AUC$_{0-24h}$ was 53 ng * hours/ml.

Finasteride has been recovered in cerebral spinal fluid, however the drug is not believed to be especially concentrated in the cerebrospinal fluid. A very small quantity of finasteride has also been discovered in seminal fluid.

**Metabolism:**
Finasteride is primarily metabolised by, but does not affect, cytochrome P450 3 A4. Following the addition of radioactively marked finasteride, two
metabolites of finasteride have been identified, which have a low 5-alpha-reductase inhibiting effect.

Elimination:
Following administration of radioactively marked finasteride, approximately 39% (32-46%) of the given dose is excreted in the urine in the form of metabolites. Practically no unchanged finasteride is recovered in the urine and 57% (51-64%) of the total dose is excreted unchanged in faeces. Clearance is approximately 165 ml/min (70-279 ml/min). The elimination rate diminishes somewhat with age. The mean terminal plasma time to half-life is 5-6 hours (3-14 hours) (8 hours in men >70, range 6-15 hours). These observations lack clinical significance, for which reason a reduction in dose is not warranted.

Hepatic impairment:
The effects on the pharmacokinetics of finasteride in hepatic impairment have not been studied.

Renal impairment:
In patients with chronic renal failure, with creatinine clearance between 9-55ml/min, AUC, maximum plasma concentration, time to half-life and degree of protein binding were unchanged by finasteride following a single dose of radioactively marked finasteride comparable with the values attained 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.

In the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately 6 hours in men aged 18-60 years to 8 hours in men aged more than 70 years. This is of no clinical significance and does not warrant a reduction in dosage.

5.3 Preclinical safety data
Current studies relating to general toxicity, genotoxicity and carcinogenicity did not demonstrate any special risks to humans.

Reproduction toxicology studies on male rats have not revealed decreased prostatic and seminal vesicular weights, reduced secretion from accessory sex glands and a reduction of fertility index (caused by the pharmacological effects of finasteride). The clinical relevance of these findings is unknown.

As with other 5-alpha-reductase inhibitors, feminisation of male rat foetuses has been observed with administration of finasteride during pregnancy. When finasteride was administered to primates during pregnancy, no evidence of feminisation of male foetuses was observed with exposure in blood well in excess of expected levels via human seminal fluid. It is unlikely that male foetuses will be negatively affected by transference of finasteride via seminal fluid.
In animal developmental studies, dose-dependent 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 alpha-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 alpha-reductase.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Microcrystalline cellulose
Pregelatinised maize starch
Sodium starch glycolate
Sodium lauril sulphate
Magnesium stearate
Hyromellose
Macrogol stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
No special storage requirements.

6.5 Nature and contents of container
PVC/PVDC/A1 blister packs containing 20, 28, 30, 50, 100 film-coated tablets or 98 film-coated tablets as calendar pack size or 50x1, 100x1 as unit doses or 3 x 100 or 10 x 30 film-coated tablets as clinical pack sizes HDPE container with polypropylene cap, 100 tablets. Not all packsizes may be marketed.

6.6 Special precautions for disposal
Women should not handle crushed or broken tablets when they are or may potentially be pregnant due to potential absorption of finasteride with subsequent potential risk to a male foetus (see section 4.6). The tablets are film-coated in order to prevent contact with the active ingredients under normal handling, subject to the condition that they are not crushed or broken.
MARKETING AUTHORISATION HOLDER
esparma GmbH
LangeGöhren 3
39171 Osterweddingen
Germany

MARKETING AUTHORISATION NUMBER(S)
PL 28309/0001

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/05/2007

DATE OF REVISION OF THE TEXT
21/05/2007
Module 3

Product Information Leaflet
Patient Information Leaflet

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

In this leaflet:
1. What is in Finasteride 5mg Film-coated Tablets?
2. What is your medicine used for?
3. Before you take Finasteride 5mg Film-coated Tablets
4. How to take Finasteride 5mg Film-coated Tablets
5. Possible side effects
6. Storing Finasteride 5mg Film-coated Tablets
7. Further Information

FINASTERIDE 5 MG FILM-COATED TABLETS

1. What is in Finasteride 5mg Film-coated Tablets?

The active substance is finasteride.

Each film-coated tablet contains 5 mg finasteride.

The product also contains
Lactose monohydrate, Microcrystalline cellulose, Pregelatinised maize starch, Sodium starch glycolate, Sodium lauril sulphate, Magnesium stearate, Hypromellose, Macrogol stearate

Marketing Authorisation Holder and Manufacturer
espera GmbH, Lange Gohren 3, D-29171 Ostercappeln, Germany

2. What is your medicine used for?

Finasteride belongs to a group of medicines called testosterone-5α-reductase inhibitors.

Finasteride 5mg Film-coated Tablets can be used to treat and control benign prostatic hyperplasia (BPH) in patients with an enlarged prostate. Finasteride may reduce the swelling, which might improve the flow of urine and reduce the need for surgery.

3. Before you take Finasteride 5mg Film-coated Tablets?

Do not take this medicine if you are allergic to finasteride or to any of the ingredients listed above.

The condition for which Finasteride 5mg Film-coated Tablets is prescribed occurs only in men. The tablets must not be taken by women and children.

What else should you know before taking Finasteride 5mg Film-coated Tablets?

Attention BPH is not cancer and does not lead to cancer, but the two conditions can be present at the same time. Before starting you on Finasteride 5mg Film-coated Tablets, it is likely that your doctor will perform some tests to check whether you have prostate cancer. Your doctor will evaluate your symptoms and their possible causes. Talk to your doctor if you have any questions.

Finasteride 5mg Film-coated Tablets can affect a blood test called PSA. If you have a PSA test done tell your doctor that you are taking Finasteride 5mg Film-coated Tablets.

Driving and using machines
There are no data to suggest that Finasteride 5mg Film-coated Tablets affect the ability to drive or use machines.

Important information about some of the ingredients of Finasteride 5 mg Film-coated Tablets
Finasteride 5 mg Film-coated Tablets contain lactose monohydrate.
If you do not tolerate some types of sugar you should contact your doctor before you take this medicine.

**Pregnancy**

If the active ingredient in Finasteride 5mg Film-coated Tablets is absorbed by a woman who is pregnant with a male baby it may affect the normal development of the baby’s sex organs. Therefore, women who are or may be pregnant should not be exposed to Finasteride 5mg Film-coated Tablets. They should not take Finasteride 5mg Film-coated Tablets. In addition, they must not handle broken or crushed tablets or be exposed to the drug through sexual contact with a man taking Finasteride 5mg Film-coated Tablets. Therefore, if your sexual partner is or may be pregnant, you must avoid exposing her to your semen which could contain a tiny amount of the drug - for example, by using a condom during sexual activity. If a woman who is pregnant comes into contact with the active ingredient in Finasteride 5mg Film-coated Tablets, a doctor should be consulted. Whole Finasteride 5mg Film-coated Tablets are coated to prevent contact with the active ingredient during normal handling.

**Breast Feeding**

Finasteride is only intended for men. It is not known if finasteride is excreted in breast milk.

**Take special care with Finasteride 5mg Film-coated Tablets**

• if you have difficulty emptying your bladder completely or a greatly reduced flow of urine, you should be examined by your doctor before you start taking Finasteride 5mg Film-coated Tablets to exclude other obstructions in the urinary tract.
Can you take Finasteride 5mg Film-coated Tablets with other medicines?
Finasteride does not usually interfere with other medicines. However, you should always tell your doctor about any other medicines you are taking or planning to take, including any obtained without prescription.

Talk to your doctor if you have any questions.

4. How to take Finasteride 5mg Film-coated Tablets

You should take your tablets exactly as your doctor has told you. The dose is one tablet containing 5 mg Finasteride to be taken by mouth once a day with or without food.

In order to treat your symptoms and control your BPH effectively, it is important that you continue to take Finasteride 5mg Film-coated Tablets for 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 5mg Film-coated Tablets for at least six months to see if it improves your symptoms.

Finasteride works best when taken long-term.

What if you forget to take a tablet or take too many?
If you miss a dose, just carry on with the next one as usual. Do not take an extra tablet to make up. If you take too many tablets or if children have taken this medicine by accident, contact your doctor immediately.

If you stop taking Finasteride 5mg Film-coated Tablets
Although an improvement is often noticed after a short time, it may be necessary to continue the treatment for at least 6 months. Do not alter the dose or stop treatment without asking your doctor.

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

5. Possible side effects

Like any medicine Finasteride 5mg Film-coated Tablets may have unintended or unwanted effects.

The most frequent side effects are impotence (inability to obtain an erection) and decreased sex drive. These effects usually occur at the beginning of the treatment and in most patients they are short-term.

Other side effects that may occur have been listed by body systems and frequency.

The frequencies are defined as:

<table>
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<td>Common</td>
<td>less than 1 in 10 but more than 1 in 100 patients</td>
</tr>
<tr>
<td>Uncommon</td>
<td>less than 1 in 100 but more than 1 in 1,000 patients</td>
</tr>
<tr>
<td>Rare</td>
<td>less than 1 in 1,000 but more than 1 in 10,000 patients</td>
</tr>
<tr>
<td>Very rare</td>
<td>less than 1 in 10,000 patients, including isolated reports</td>
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Skin disorders
Uncommon: Skin rash
Rare: Pruritus (itching), urticaria (hives)

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

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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. If possible note what you experienced and when it started and how long it lasted.

Stop taking Finasteride 5mg Film-coated Tablets and contact your doctor immediately if you develop any of the following symptoms: swelling of the face, tongue or face, swallowing difficulties or urticaria and difficulties of breathing.

6. Storing Finasteride 5mg Film-coated Tablets

Keep your tablets out of the reach and sight of children.

Keep your tablets in the original container.
If you have been given a calendar pack, do not remove the tablets from the blister until you are ready to take the medicine.

Do not take the tablets past the expiry date which is clearly marked on the pack and blister.

7. Further Information

Finasteride 5mg Film-coated Tablets are available in pack sizes with

- 20, 28, 30, 50, 100 film-coated tablets
- or 98 film-coated tablets as calendar pack size
- or 50x1, 100x1 film-coated tablets as unit doses.

If you have any other questions after you have read it, ask your doctor or pharmacist, who will give you further information.

This leaflet was revised: November 2006
Module 4

Labelling

Carton (30 tablets):
Carton (50 tablets):
Carton (98 tablets, calendar pack):
Carton (100 tablets):
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Finasteride 5mg Film-coated Tablets in the treatment of benign prostatic hyperplasia could be approved.

EXECUTIVE SUMMARY

Problem statement
This application for marketing authorisation (MAA), submitted via the decentralised procedure with the UK as RMS, concerns a generic version of finasteride under the trade name Finasteride 5mg Film-coated Tablets. The application is submitted under article 10.1 of Council Directive 2001/83/EC, as amended, claiming to be a generic to the reference medicinal product Proscar, marketed by Merck Sharp Dohme, Germany and Proscar, marketed by Merck and Co., Inc., USA.

About the product
The active compound in these tablets is finasteride, a competitive and specific inhibitor of the enzyme steroid type II 5α-reductase, which catalyses the 5α-reduction of testosterone to the more potent androgen dihydro-testosterone (DHT). Finasteride is chemically similar to testosterone, but does not affect the binding of testosterone or DHT to the androgen receptor, nor does it possess any steroid hormone-related properties. Therefore, the major effect of finasteride is to decrease prostatic and circulating DHT levels.

Finasteride 5 mg Film-coated Tablets is considered a generic of the reference medicinal product, Proscar, as it satisfies the criteria of having the same qualitative and quantitative composition in terms of active ingredients, the same pharmaceutical form and is considered bioequivalent to the reference medicinal product.

General comments on the submitted dossier
For this application reference is made to the German product, Proscar, marketed by Merck Sharp Dohme, Germany. The German reference product has been licensed in Germany since September 1994.

To support the application, the applicant has submitted one bioequivalence study to prove bioequivalence comparing the test product Finasteride 5mg Film-coated Tablets with the reference products, Proscar Germany and Proscar USA. The submitted dossier is adequate and sufficient.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The applicant states that the study was conducted in accordance with Good Clinical Practices, Good Laboratory Practices, other applicable regulations and implemented internal standard operation procedures. Review of the dossier revealed no evidence of
non-compliance with GLP or GCP.

Scientific Overview and Discussion

Quality aspects
The product is formulated as immediate release, film-coated tablets. The tablets are packaged in blister packs or HDPE containers.

Drug substance
The drug substance, finasteride, is the subject of a European Pharmacopoeia monograph. The drug substance specification is based on the Ph Eur monograph. The analytical methods have been validated in accordance with current guidelines as appropriate.

Drug product
The drug product is a film-coated tablet, which is manufactured from conventional pharmaceutical excipients using a standard, direct compression method. Development of the formulation has been described. Comparative studies between the reference product and the proposed product show essential similarity in terms of dissolution and impurity profiles. The manufacturing method has been satisfactorily validated using production scale batches from each of the proposed manufacturing sites. The finished product specification is based on relevant development and stability studies. Appropriate validation data has been provided for the analytical methods. Batch analyses data support the proposed finished product specification. Stability studies have been carried out in accordance with ICH guidelines and data presented support the proposed three year shelf-life.

Non clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of finasteride are well known. As finasteride is a widely used, well-known active substance, no further studies are required and the applicant provides none. Rather, an overview based on a literature review is provided, which is appropriate.

Critical evaluation of the Non-Clinical Overview and Summary
There are no objections to approval of Finasteride 5mg Film-coated Tablets from a non-clinical point of view.

Clinical aspects

Pharmacokinetics
To support the application, the applicant has submitted a bioequivalence study to prove bioequivalence between the test Finasteride 5mg Film-coated Tablets and Proscar Filmtabletten (Merck Sharp Dohme, Germany). The study is a randomised, single-dose, 3-way crossover study. The primary parameters on which bioequivalence is based are AUC 0-t and Cmax.

After a single-dose administration of the finasteride oral test formulation and the reference formulations in healthy male subjects, the pharmacokinetic parameters were similar between both treatments. In the fasted state, the 90% CIs of the
The pharmacokinetic parameters AUC<sub>0-t</sub> (88.94–100.98 (USA) and 94.41–107.19 (Germany)) and C<sub>max</sub> (87.26–96.17 (USA) and 91.75–101.12 (Germany)) were within the bioequivalence acceptance range of 80%–125%. Therefore, the results obtained from this study demonstrate that the test formulation is bioequivalent to the reference formulations in fasted state.

The application contains an adequate review of published clinical data and bioequivalence, with respect to extent and rate of absorption of Finasteride 5mg Film-coated Tablets.

Clinical safety
A total of 24 adverse events occurred during the study (nine following administration of test product, four following administration of Proscar USA and 11 following administration of Proscar Germany). The most commonly reported adverse events were hot flushes and scratching, reported on 4 and 3 occasions, respectively.

Of the 24 post-dose adverse events, 20 were graded as mild and four as moderate, the relationship to the study medication was judged as “remote” in nine cases and “unrelated” in 15 cases. There were no deaths or serious adverse events.

The safety results do not elicit new safety concerns with regard to the test product. In addition, there is vast clinical experience with other finasteride containing medicinal products indicating a good tolerability and safety of the active substance.

BENEFIT RISK ASSESSMENT
Satisfactory information is provided in the quality dossier and there are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

There are no objections to approval of Finasteride 5mg Film-coated Tablets from a non-clinical point of view.

The applications contain an adequate review of published clinical data. Based on the submitted bioequivalence study Finasteride 5 mg Film-coated Tablets is considered bioequivalent to 5 mg tablets of Proscar Germany and Proscar USA.
Overall conclusion

QUALITY

The important quality characteristics of Finasteride 5 mg 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 preclinical data is needed for this application.

No new or unexpected safety concerns arise from these applications.

EFFICACY

Clinical studies have demonstrated the efficacy of Finasteride 5 mg Film-coated Tablets in the treatment and control of benign prostatic hyperplasia (BPH) in patients with enlarged prostate.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.