Public Assessment Report
Mutual Recognition Procedure

FINASTERIDE 1 MG FILM-COATED TABLETS

UK/H/4251/001/MR
UK Licence No: PL 00289/0826

TEVA UK LIMITED
LAY SUMMARY

On 10\textsuperscript{th} August 2009, the UK granted Teva UK Limited a Marketing Authorisation (licence) for Finasteride 1 mg Film-coated Tablets.

On 19\textsuperscript{th} January 2011, Teva UK Limited was granted a Marketing Authorisation (licence) in Denmark, Germany, Finland, France, Hungary, Italy, The Netherlands, Poland, Portugal, Spain and Sweden for Finasteride 1 mg Film-coated Tablets.

The active ingredient in this medicine is finasteride.

Finasteride 1 mg Film-coated Tablets belong to a group of medicines called testosterone 5-alpha reductase inhibitors. Finasteride is used in the treatment of men with male pattern hair loss (androgenetic alopecia), to increase hair growth and prevent hair loss.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Finasteride 1 mg Film-coated Tablets outweigh the risks; hence this Marketing Authorisation has been granted.
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Module 1

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<tr>
<th><strong>Product Name</strong></th>
<th>Finasteride 1 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Finasteride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>1 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>TEVA UK Ltd Brampton Road, Hampden Park Eastbourne, BN22 9AG England</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Denmark (DK), Germany (DE), Finland (FI), France (FR), Hungary (HU), Italy (IT), The Netherlands (NL), Poland (PL), Portugal (PT), Spain (ES) and Sweden (SE).</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/4251/001/MR</td>
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<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 90 – 19th January 2011</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1 mg of finasteride.

Excipients:
Each tablet contains 112 mg of lactose monohydrate (see section 4.4).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Brown, round film-coated tablets, debossed “FNT1” on one side and plain on the other.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Early stages of androgenetic alopecia in men. Finasteride stabilizes the process of androgenetic alopecia in men 18-41 years of age. Efficacy in bitemporal recession and end-stage hair loss has not been established.

4.2 Posology and method of administration
1 tablet (1 mg) daily with or without food.

There is no evidence that an increase in dosage will result in increased efficacy.

Efficacy and duration of treatment should continuously be assessed by the treating physician. Generally, three to six months of once daily treatment are required before evidence of stabilisation of hair loss can be expected. Continuous use is recommended to sustain benefit. If treatment is stopped, the beneficial effects begin to reverse by 6 months and return to baseline by 9 to 12 months.

No dosage adjustment is required in patients with renal insufficiency.

Children and adolescents
The safety and efficacy of finasteride in children and adolescents aged less than 18 years have not been established. No data are available.

4.3 Contraindications
Contra-indicated in women: see sections 4.6 and 5.1
Hypersensitivity to finasteride or to any of the excipients

4.4 Special warnings and precautions for use
Finasteride should not be used in children. There are no data demonstrating efficacy or safety of finasteride in children under the age of 18.

In clinical studies with finasteride in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/ml at baseline to 0.5 ng/ml at month 12. Doubling the PSA level in men taking finasteride should be considered before evaluating this test result.

Long-term data on fertility in humans are lacking, and specific studies in subfertile men have not been conducted. The male patients who were planning to father a child were initially excluded from clinical trials. Although animal studies did not show relevant negative effects on fertility, spontaneous reports of infertility and/or poor seminal quality were received post-marketing. In some of these reports, patients had other risk factors that might have contributed to infertility. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride.

The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied.
Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Finasteride is metabolised via, but does not affect, the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4 will affect the plasma concentration of finasteride. However, based on established safety margins, any increase due to concomitant use of such inhibitors is unlikely to be of clinical significance.

4.6 Pregnancy and lactation

Pregnancy

Finasteride is suspected to cause serious birth defects when administered during pregnancy. It is contraindicated for use in women due to the risk in pregnancy.

Small amounts of finasteride have been recovered from semen in subjects receiving finasteride 5 mg/day. It is not known whether a male fetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride. When the patient’s sexual partner is or may potentially be pregnant, the patient is recommended to minimise exposure of his partner to semen.

Lactation

It is not known whether finasteride is excreted in human milk.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed.

4.8 Undesirable effects

The adverse reactions during clinical trials and/or post-marketing use are listed in the table below. Frequency of adverse reactions is determined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Not known</th>
<th>Hypersensitivity reactions, including rash, pruritus, urticaria and swelling of the lips and face</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Palpitation</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Increased hepatic enzymes</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Uncommon</td>
<td>Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate), decreased libido*</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Breast tenderness and enlargement, testicular pain, infertility**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>** see section 4.4</td>
</tr>
</tbody>
</table>

* Incidences presented as difference from placebo in clinical studies at Month 12.

Drug-related undesirable effects were more common in the finasteride-treated men than the placebo-treated men, with frequencies during the first 12 months of 3.8% vs 2.1%, respectively. The incidence of these effects decreased to 0.6% in finasteride-treated men over the following four years. Approximately 1% of men in each treatment group discontinued due to drug-related sexual adverse experiences in the first 12 months, and the incidence declined thereafter.

In addition, the following have been reported in post-marketing use: persistence of erectile dysfunction after discontinuation of treatment with finasteride, male breast cancer (see section 4.4).

4.9 Overdose

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months (n=71) did not result in dose-related undesirable effects.
PAR Finasteride 1 mg Film-Coated Tablets

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other dermatological preparations, other dermaticals
ATC code: D11AX10

Finasteride is a 4-azasteroid which inhibits human type II 5α-reductase (present within the hair follicles) with greater than 100-fold selectivity over human type I 5α-reductase, and blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT).

In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT. Finasteride inhibits a process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process.

Studies in men
The efficacy of finasteride was demonstrated in 3 studies in 1879 men aged 18 to 41 years with mild to moderate, but not complete, vertex hair loss and frontal/mid-area hair loss. In these studies, hair growth was assessed using 4 separate measures including hair count, ratings of photographs of the head by an expert panel of dermatologists, investigator assessment, and patient self-assessment.

In the two studies in men with vertex hair loss, treatment with finasteride was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning at 3 to 6 months. While hair improvement measures compared to baseline in men treated with finasteride were generally greatest at 2 years and gradually declined thereafter (e.g. hair count in a representative 5.1 cm² area was increased 88 hairs from baseline at 2 years and 38 hairs from baseline at 5 years), hair loss in the placebo group progressively worsened compared to baseline (decrease of 50 hairs at 2 years and 239 hairs at 5 years). Thus, although improvement compared to baseline in men treated with finasteride did not increase further after 2 years, the difference between treatment groups continued to increase throughout the 5 years of the studies. Treatment with finasteride for 5 years resulted in stabilisation of hair loss in 90% of men based on photographic assessment and in 93% based on investigator assessment. In addition, increased hair growth was observed in 65% of men treated with finasteride based on hair counts, in 48% based on photographic assessment, and in 77% based on investigator assessment. In contrast, in the placebo group, gradual hair loss over time was observed in 100% of men based on hair counts, in 75% based on photographic assessment, and in 38% based on investigator assessment. In addition, patient self-assessment demonstrated significant increases in hair density, decreases in hair loss, and improvement in appearance of hair after treatment over 5 years with finasteride (see table below).

<table>
<thead>
<tr>
<th>Percent of patients improved as assessed by each of the 4 measures</th>
<th>Year 1 †</th>
<th>Year 2 ††</th>
<th>Year 5 ††</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hair count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>(n=679) 86</td>
<td>(n=433) 83</td>
<td>(n=219) 65</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=672) 42</td>
<td>(n=47) 28</td>
<td>(n=15) 0</td>
</tr>
<tr>
<td><strong>Global photographic assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>(n=720) 48</td>
<td>(n=508) 66</td>
<td>(n=279) 48</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=709) 7</td>
<td>(n=55) 7</td>
<td>(n=16) 6</td>
</tr>
<tr>
<td><strong>Investigator assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>(n=748) 65</td>
<td>(n=535) 80</td>
<td>(n=271) 77</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=747) 37</td>
<td>(n=60) 47</td>
<td>(n=13) 15</td>
</tr>
<tr>
<td><strong>Patient self-assessment: satisfaction with appearance of hair overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride</td>
<td>(n=750) 39</td>
<td>(n=535) 51</td>
<td>(n=284) 63</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=747) 22</td>
<td>(n=60) 25</td>
<td>(n=15) 20</td>
</tr>
</tbody>
</table>

†: Randomisation 1:1 finasteride to placebo
††: Randomisation 9:1 finasteride to placebo

In a 12-month study in men with frontal/mid-area hair loss, hair counts were obtained in a representative 1 cm² area (approximately 1/5 the size of the area sampled in the vertex studies). Hair counts, adjusted to a 5.1 cm² area, increased by 49 hairs (5%) compared to baseline and by 59 hairs (6%) compared to placebo. This study also demonstrated significant improvements in patient self-
assessment, investigator assessment, and ratings of photographs of the head by an expert panel of dermatologists.

Two studies of 12 and 24 weeks' duration showed that a dose 5-fold the recommended dose (finasteride 5 mg daily) produced a median decrease in ejaculate volume of approximately 0.5 ml (-25%) compared with placebo. This decrease was reversible after discontinuation of treatment. In a study of 48 weeks' duration, finasteride 1 mg daily produced a median decrease in ejaculate volume of 0.3 ml (-11%) compared with a 0.2 ml (-8%) decrease for placebo. No effect was observed on sperm count, motility or morphology. Longer-term data are not available. It has not been feasible to undertake clinical studies which directly elucidate possible negative effects on fertility. However, such effects are judged as very unlikely (see also section 5.3).

Studies in women
Lack of efficacy was demonstrated in post-menopausal women with androgenetic alopecia who were treated with finasteride 1 mg for 12 months.

5.2 Pharmacokinetic properties
Bioavailability
The oral bioavailability of finasteride is approximately 80% and is not affected by food. Maximum finasteride plasma concentrations are reached approximately 2 hours after dosing and the absorption is complete after 6 to 8 hours.

Distribution
Protein binding is approximately 93%. The volume of distribution is approximately 76 litres (44-96 l).

At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/ml and was reached 1 to 2 hours postdose; AUC (0-24 hr) was 53 ng x hr/ml.

Finasteride has been recovered in the cerebrospinal fluid (CSF), but the drug does not appear to concentrate preferentially to the CSF. A very small amount of finasteride has also been detected in the seminal fluid of subjects receiving the drug. Studies in rhesus monkeys showed that this amount is not considered to constitute a risk to the developing male fetus (see sections 4.6 and 5.3).

Biotransformation
Finasteride is metabolised primarily via but does not affect the cytochrome P450 3A4 system. Following an oral dose of 14C-finasteride in man, two metabolites of the drug were identified that possess only a small fraction of the 5α-reductase inhibitory activity of finasteride.

Elimination
Following an oral dose of 14C-finasteride in man, approximately 39% (32-46%) of the dose was excreted in the urine in the form of metabolites. Virtually no unchanged drug was excreted in the urine and 57% (51-64%) of total dose was excreted in the faeces.

Plasma clearance is approximately 165 ml/min (70-279 ml/min).

The elimination rate of finasteride decreases somewhat with age. Mean terminal plasma half-life is approximately 5-6 hours (3-14 hours) (in men more than 70 years of age 8 hours (6-15 hours)). These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

Hepatic insufficiency
The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied.

Renal insufficiency
In patients with chronic renal impairment, with creatinine clearances ranging from 9-55 ml/min, area under the curve, maximum plasma concentrations, half-life, and protein binding of unchanged finasteride after a single dose of 14C-finasteride were similar to values obtained in health volunteers.

5.3 Preclinical safety data
Mutagenicity/carcinogenicity
Studies on genotoxicity and carcinogenicity have not revealed any hazards for humans.

Reproduction-disturbing effect including fertility
The effects on embryonic and fetal development have been studied in rats, rabbits and rhesus monkeys. In rats treated with 5-5,000 times the clinical dose, a dose-related occurrence of hypospadias has been observed in male fetuses. In rhesus monkeys, treatment with oral doses of 2 mg/kg/day has also resulted in external genital abnormalities.

Intravenous doses of up to 800 ng/day in rhesus monkeys have not shown any effects on male fetuses. This represents at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day (see section 5.2).

In the rabbit study, the fetuses were not exposed to finasteride during the period critical for genital development.

Neither ejaculation volume, sperm count nor fertility were affected in the rabbit after treatment with 80 mg/kg/day, a dose that in other studies is shown to have pronounced weight-lowering effects on accessory sexual glands. In rats treated for 6 and 12 weeks with 80 mg/kg/day (approximately 500 times the clinical exposure) no effect on fertility was observed. After 24-30 weeks' treatment some reduced fertility and pronounced weight reduction of prostate and seminal vesicle were seen. All changes were reversible within a 6-week period. The reduced fertility has been shown to be due to impaired seminal plug formation, an effect that has no relevance to man. The development of the newborns and their reproduction capacity at the age of sexual maturation were without remark. After insemination of female rats with epididymis sperms from rats treated for 36 weeks with 80 mg/kg/day no effect was seen on a number of fertility parameters.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core
Lactose monohydrate (200 mesh)
Starch, pregelatinised (maize)
Sodium laurilsulfate
Sodium starch glycolate (Type A)
Povidone (K30)
Cellulose, microcrystalline
Magnesium stearate

Coating
Hypromellose 6 cP (E464)
Titanium dioxide (E171)
Macrogol 6000
Macrogol 400
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special precautions for storage.

6.5 Nature and contents of container
Transparent PVC/PVdC-aluminium blisters.
Blister packs of 7, 28, 30, 50 (Hospital Packs), 84, 98 and 100 Film-coated Tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Crushed or broken tablets of finasteride should not be handled by women when they are or may potentially be pregnant because of the possibility of absorption of finasteride and subsequent potential risk to a male fetus (see section 4.6). Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.
7 MARKETING AUTHORIZATION HOLDER
TEVA UK Ltd
Brampton Road, Hampden Park
Eastbourne, BN22 9AG
England

8 MARKETING AUTHORIZATION NUMBER(S)
PL 00289/0826

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
10/08/2009

10 DATE OF REVISION OF THE TEXT
06/07/2011
Module 3
Patient Information Leaflet

The Patient Information Leaflet (PIL) below is the leaflet agreed at the end of the mutual recognition procedure. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL for review to the regulatory authority before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Finasteride 1 mg Film-Coated Tablets

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get 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 1 mg Film-Coated Tablets is and what it is used for
2. Before you take Finasteride 1 mg Film-Coated Tablets
3. How to take Finasteride 1 mg Film-Coated Tablets
4. Possible side effects
5. How to store Finasteride 1 mg Film-Coated Tablets
6. Further information

1. WHAT FINASTERIDE 1 MG FILM-COATED TABLETS IS AND WHAT IT IS USED FOR

- Finasteride 1 mg Film-Coated Tablets contain a medicine called finasteride.
- Finasteride is used for the treatment of male pattern hair loss (also known as androgenetic alopecia). If after reading this leaflet, you have any questions about male pattern hair loss, ask your doctor.
- Male pattern hair loss is a common condition thought to be caused by a combination of genetic factors and a particular hormone, called dihydrotestosterone (DHT). DHT contributes to shortening of the growth phase of the hair and to thinning of the hair.
- In the scalp, finasteride specifically lowers the levels of DHT by blocking an enzyme (type 2 5-alpha reductase) that converts testosterone to DHT. Only men with mild to moderate, but not complete hair loss can expect to benefit from the use of Finasteride. In most of the men treated with finasteride for 5 years, the progression of hair loss was slowed, and at least half of these men also had some kind of improved hair growth.

2. BEFORE YOU TAKE FINASTERIDE 1 MG FILM-COATED TABLETS

Do not take Finasteride if
- You are a woman (because this medicine is for men, see Pregnancy). It has been shown in clinical trials that finasteride does not work in women with hair loss.
- You are allergic (hypersensitive) to finasteride or any of the other ingredients of this medicine (listed in section 6). If you are not sure, talk to your doctor or pharmacist.

Take special care with Finasteride
- Finasteride should not be taken by children and teenagers under the age of 18 years.
- are to have a blood test called prostate-specific antigen (PSA) tell your doctor or pharmacist that you are taking Finasteride as it may affect the results.
- Tell your doctor or pharmacist about any medical problems you have or have had, and about any allergies.
Taking other medicines

Finasteride can usually be taken with other medicines. Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Finasteride with food and drink

Finasteride can be taken with or without food.

Pregnancy

- Finasteride is for the treatment of male pattern hair loss in men only.
- **Women must not use Finasteride due to the risk of pregnancy.**
- **Do not touch crushed or broken tablets of Finasteride if you are a woman who is pregnant or may potentially be pregnant.**
- If the active ingredient of Finasteride is absorbed after oral use or through the skin by a woman who is pregnant with a male baby, this may cause the male baby to be born with abnormalities of the sex organs.
- If a woman who is pregnant comes into contact with the active ingredient of Finasteride, a doctor should be consulted.
- Finasteride tablets are coated and will prevent contact with the active ingredient during normal use.

If your sexual partner is or may be pregnant, you must avoid exposing her to your semen (e.g. by using a condom).

If you have questions, ask your doctor.

Driving and using machines

Finasteride is not expected to or known to affect your ability to drive or operate machinery.

Important information about some of the ingredients of Finasteride

Patients who are intolerant to lactose should note that Finasteride tablets contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. **HOW TO TAKE FINASTERIDE 1 MG FILM-COATED TABLETS**

Always take Finasteride exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Taking this medicine

The usual dose is one tablet each day.
The tablets can be taken with or without food.
Finasteride will not work faster or better if you take it more than once a day.

Your doctor will help you to determine if Finasteride is working for you. It is important to take Finasteride for as long as your doctor prescribes it. Finasteride can only work over the long term if you continue taking it.
If you take more Finasteride than you should

If you take too many tablets by mistake, talk to your doctor promptly.

If you forget to take Finasteride

If you forget to take a tablet, skip the missed dose. Take the next one as usual. Do not take a double dose to make up for the forgotten dose.

If you stop taking Finasteride

It may take 3 to 6 months for the full effect to develop. It is important to keep taking Finasteride as long as your doctor tells you. If you stop taking Finasteride, you are likely to lose the hair you have gained within 9 to 12 months.

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 can cause side effects, although not everybody gets them.

The side effects have usually been temporary with continued treatment or disappeared when treatment is stopped:

Uncommon (affects 1 to 10 users in 1,000)

- Less desire to have sex
- Difficulty having an erection
- Problems with ejaculation such as a decrease in the amount of semen released

Frequency not known

- Allergic reactions such as rash, itching, lumps under your skin (hives) and swelling of your lips and face
- Breast swelling or tenderness
- Pain in the testicles
- Faster heartbeat
- Persistent difficulty having an erection after discontinuation of treatment
- Infertility has been reported in men who took finasteride for a long time and had other risk factors that may affect fertility. Normalisation or improvement of seminal quality has been reported after discontinuation of finasteride. Long-term clinical studies about the effect of finasteride on fertility in men have not been conducted.
- Elevated liver enzymes.

You should promptly report to your doctor any changes in the breast tissue such as lumps, pain, enlargement of the breast tissue or nipple discharge as these may be signs of a serious condition, such as breast cancer.

Stop taking Finasteride and talk to your doctor immediately if you have any of the following symptoms:

- Swelling of your face, tongue or throat
- Difficulty swallowing
- Lumps under your skin (hives)
- Breathing difficulties.
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 1 MG FILM-COATED TABLETS**

Keep out of the reach and sight of children. Do not use Finasteride after the expiry date that is stated on the blister and carton. The expiry date refers to the last day of that month. This product does not require any special storage precautions. Medicines should not be disposed of via waste water 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 1mg Film-Coated Tablets contain

- The active ingredient is finasteride.
- The other ingredients are lactose monohydrate, pregelatinised maize starch, sodium laurilsulfate, sodium starch glycolate (type A), povidone, microcrystalline cellulose, magnesium stearate, hypromellose 6 eP (E464), titanium dioxide (E171), macrogol 6000, macrogol 400, iron oxide red (E172) and iron oxide yellow (E172).

What Finasteride 1mg Film-Coated Tablets look like and the contents of the pack

- Finasteride 1 mg Film-Coated tablets are brown and round in shape. The tablets are marked with “FNT1” on one side and plain on the other.
- The product is available in blister packs of 7, 28, 30, 50 (hospital packs), 84, 98 and 100 film-coated tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

TEVA UK Limited, Eastbourne, BN22 9AG.

This leaflet was last revised: February 2011

PL 00289/0826
Module 4
Labelling

The labelling below is the label agreed at the end of the mutual recognition procedure. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the product.

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Finasteride 1 mg Film-Coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of finasteride.

3. LIST OF EXCIPIENTS

Also contains lactose
Please see the enclosed leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

- 7 film-coated tablets
- 28 film-coated tablets
- 30 film-coated tablets
- 50 film-coated tablets (Hospital Packs)
- 84 film-coated tablets
- 98 film-coated tablets
- 100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

FOR USE BY MEN ONLY.
8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

TEVA UK Ltd, Eastbourne, BN22 9AG.

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 00289/0826

13. **BATCH NUMBER**

LOT

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor.

16. **INFORMATION IN BRAILLE**

Finasteride 1 mg Film-Coated Tablets
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride 1 mg Film-Coated Tablets</td>
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<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva UK Ltd, Eastbourne, BN22 9AG</td>
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<table>
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<tr>
<th>3. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP:</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
A Marketing Authorisation via a National Procedure for Finasteride 1mg Film-coated Tablets was granted in the UK on 10th August 2009.

Based on the review of the data on quality, safety and efficacy, Denmark, Germany, Finland, France, Hungary, Italy, The Netherlands, Poland, Portugal, Spain and Sweden and the UK (reference member state) considered that the application for Finasteride 1mg Film-coated Tablets could be approved via the Mutual Recognition Procedure. This prescription only medicine (POM) is indicated for the early stages of androgenetic alopecia in men. Finasteride stabilizes the process of androgenetic alopecia in men 18-41 years of age.

This application for Finasteride 1mg Film-coated Tablets was submitted according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Chibro-Proscar 5 mg comprimé pelliculé, approved in the EEA to Laboratoires Merck Sharp Dohme-Chibret on 22nd June 1992.

The equivalent and the product used as the reference product in the bioequivalence study is Proscar® 5 mg Tablets (PL 00025/0279), approved in the UK to Merck Sharp & Dohme Limited on 27th May 1992.

The UK reference product is Propecia® 1 mg Tablets (00025/0351), approved in the UK to Merck Sharp & Dohme Limited on 20th September 1999.

Finasteride is a competitive inhibitor of human 5-alpha-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). The tablets are indicated for the treatment of men with male pattern hair loss (adrogenetic alopecia) to increase hair growth and prevent further hair loss. The recommended adult dose is one tablet daily, with or without food. Efficacy in bitemporal recession and end-stage hair loss has not been established.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of finasteride is well-established.

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.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the
notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for absence of a Risk Management Plan.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Finasteride 1 mg Film-coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Finasteride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>other dermatological preparations, other dermaticals (D11AX10)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>1 mg Film-coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4251/001/MR</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom (UK)</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Denmark (DK), Germany (DE), Finland (FI), France (FR), Hungary (HU), Italy (IT), The Netherlands (NL), Poland (PL), Portugal (PT), Spain (ES) and Sweden (SE).</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 00289/0826</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder       | TEVA UK Ltd  
Brampton Road, 
Hampden Park 
Eastbourne, 
BN22 9AG 
England |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Drug substance

INN: Finasteride
Chemical name: (1) \(N-(1,1\text{-Dimethylmethyl})-3\text{-oxo-4-aza-5α-androst-1-ene-17b-carboxamide}\) (Ph Eur name)

(2) \(N\text{-tert-Butyl-3-oxo-4-aza-5α-androst-1-ene-17 β-carboxamide}\)

(3) \((5α-17β)-N-(1,1\text{-Dimethylmethyl})-3\text{-oxo-4-azaandrost-1-ene-17-carboxamide}\)

(4) \(17-β-(N\text{-tert-butylcarbomyl})-4\text{-aza-5α-androst-1-en-3-one}\)

Structural formula:

![StructuralFormula.png](attachment:StructuralFormula.png)

Molecular formula: \(\text{C}_{23}\text{H}_{36}\text{N}_{2}\text{O}_{2}\)
Molecular weight: 372.6
Appearance: 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

Finasteride complies with its European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data has been supplied for the drug substance.
All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance, with suitable test methods and limits. 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. Suitable Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the drug substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product

Other Ingredients

Other ingredients inside the tablet core consist of pharmaceutical excipients lactose monohydrate (200 mesh), pregelatinised starch (maize), sodium laurilsulfate, sodium starch glycolate (Type A), povidone (K30), microcrystalline cellulose and magnesium stearate.

The tablet coating consists of Opadry 03G26753 brown and consists of hypromellose 6 cP (E464), titanium dioxide (E171), macrogol 6000, macrogol 400, red iron oxide (E172) and yellow iron oxide (E172).

With the exception of red iron oxide (E172) and yellow iron oxide (E172), all excipients comply with their respective European Pharmacopoeia monographs.

Red iron oxide (E172) and yellow iron oxide (E172) comply with in-house specifications.

With the exception of lactose monohydrate, none of the excipients used contain material of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose used is sourced from healthy animals under the same conditions as milk for human consumption. The supplier has confirmed that the magnesium stearate in this product is sourced from vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to produce a safe, efficacious product containing finasteride that could be considered a generic medicinal product of Propecia® 1 mg Tablets approved in the UK to Merck Sharp & Dohme Limited on 20th September 1999.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference product.
Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The finished product is packaged in transparent polyvinyl chloride (PVC), polyvinlidene (PVdC) and aluminium blisters.

The pack sizes are 7, 28, 30, 50 (Hospital Packs), 84, 98 and 100 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 3 years with no special storage instructions.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK PIL and labelling (text only) are included in modules 3 and 4 of this report.

User testing results have been submitted for the PIL for this product. 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.

MAA forms
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of finasteride are well-known. As finasteride is widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature review is, thus, appropriate.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification has been provided for absence of an Environmental Risk Assessment.

It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics
A randomised, single-dose cross-over study to compare the bioequivalence of Finasteride 5mg Film-Coated Tablets and Proscar® (finasteride) 5mg tablets (Merck Sharp & Dohme Limited) in healthy male volunteers.

Blood samples were taken pre- and up to 30 hours post dose. There was a washout period of 7 days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for finasteride are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (ng/ml)</th>
<th>Tmax (h)</th>
<th>T1/2 (h)</th>
<th>AUC0-∞ (ng/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>32.8</td>
<td>2.0</td>
<td>5.79</td>
<td>259.65</td>
</tr>
<tr>
<td>Reference</td>
<td>32.09</td>
<td>2.26</td>
<td>5.63</td>
<td>257.45</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>93.40 – 107.99</td>
<td>-</td>
<td>-</td>
<td>90.93 – 104.78</td>
</tr>
</tbody>
</table>

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
Cmax maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC0-∞ and Cmax for finasteride lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

The applicant provided the following justifications as to why the bioequivalence study was conducted with the 5 mg strength instead of the 1 mg strength:

- The pharmaceutical products are manufactured by the same manufacturer and process.
- The strength where the sensitivity is largest to identify differences in the two products has been used to establish bioequivalence.
- The ratio between amounts of active ingredient and the excipients is the same.
- The qualitative composition of the different strengths is the same.
- The in vitro dissolution profiles are the same.
- The pharmacokinetics of finasteride are linear.

As the 5 mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 5 mg strength can be extrapolated to Finasteride 1 mg Film-coated Tablets.
EFFICACY
No new efficacy data were submitted with this application and none were required.

SAFETY
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are medically satisfactory and consistent with those for the reference product, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Form is medically satisfactory.

CONCLUSIONS
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Finasteride 1 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.

NON-CLINICAL
No new non-clinical 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 Film-coated Tablets and the reference product Proscar® 5 mg Film-coated Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with finasteride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
### Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/04/2011</td>
<td>Type II</td>
<td>To update the SPC and consequentially the PIL and labels in line with the final agreed wording following MRP. No PIL or label mock ups have been provided and assurance has been given that the product will not be marketed until these are approved by the MHRA.</td>
<td>Granted – 06/07/2011</td>
</tr>
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</table>