

Public Assessment Report
Decentralised Procedure

FINASTERIDE 1MG FILM-COATED TABLETS

Procedure No: UK/H/1279/001/DC

UK Licence No: PL 08553/0251

DR. REDDY'S LABORATORIES (UK) LIMITED

LAY SUMMARY

The MHRA granted Dr Reddy's Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Finasteride 1mg film-coated Tablets on 15th July 2009. This prescription-only medicine is used to prevent hair loss and to encourage hair growth in men, who are in the early stages of male hair loss which is also known as androgenetic alopecia (AGA).

Finasteride is a type of medicine called a 5-alpha-reductase inhibitor.

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

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Module 1

Product Name	Finasteride 1mg film-coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Finasteride
Form	Film-Coated Tablets
Strength	1mg
MA Holder	Dr Reddy's Laboratories (UK) Limited 6 Riverview Road Beverley HU17 0LD, United Kingdom
Reference Member State (RMS)	UK
CMS	Bulgaria, Italy, Romania and Spain
Procedure Number	UK/H/1279/001/DC
Timetable	Day 210 – 2 nd June 2009

Module 2

Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 1mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg of finasteride.

Excipient(s):

Each tablet also contains 44mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light brown, round biconvex film-coated tablet debossed with “FIN” on one side and “1” on reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Early stages of androgenetic alopecia in men, Finasteride 1mg Film-coated Tablets 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

Route of administration: oral use.

Men: 1mg once daily with or without food for 3-6 months before any noticeable difference is evident. There is no evidence that higher doses of finasteride result in increased efficacy.

Efficacy and duration should be continuously assessed by the treating physician. Generally, continued treatment for 3-6 months is required before stabilisation of hair loss can be expected. Continued treatment is advised to sustain benefit. If treatment is stopped, the beneficial effects begin to reverse after about 6 months, and return to baseline after 9-12months.

No data are available on the concomitant use of Finasteride with topical minoxidil for the treatment of male hair loss.

Dosage in the elderly. No dosage adjustment is required in the elderly (see section 5.2).

Dosage in renal insufficiency. Dosage adjustments are not necessary (see section 5.2)

Dosage in hepatic insufficiency. There are no data available for the use of finasteride in patients with hepatic insufficiency (see section 4.4 and 5.2).

Children: This medicine should not be administered to children (see section 4.3).

Finasteride 1 mg Film-coated Tablets is contraindicated in children (see section 4.3)

4.3 Contraindications

Known hypersensitivity to finasteride or any of the excipients.

Finasteride is contraindicated for use in women due to the risk in pregnancy (see section 4.6).

Finasteride is not indicated for use in women or children and adolescents.

Finasteride 1 mg should not be taken by men who are already taking finasteride 5 mg or any other 5 α -reductase inhibitor for benign prostatic hyperplasia or any other condition.

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.

Clinical studies have shown that Finasteride 1mg Tablets decreased mean Prostate Specific Antigen (PSA) levels from 0.7ng/ml to 0.5ng/ml at 12months. This decrease in PSA levels needs to be considered if during treatment with finasteride, a patient requires a PSA test. In this case the PSA value should be doubled before any comparison is made with untreated patients.

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.

This product contains lactose, so patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine (see section 2 and 6.1).

4.5 Interaction with other medicinal products and other forms of interaction

Finasteride is metabolized primarily 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.

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

Other concomitant therapy. Although specific interaction studies were not performed in clinical trials, a product containing finasteride was used concomitantly with ACE inhibitors, acetaminophen, acetylsalicylic acid, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Pregnancy and lactation

Finasteride is contraindicated in women who are or may potentially become pregnant (see section 4.3 and 5.3). Because of the ability of type II 5-alpha reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormalities of the external genitalia of male fetus when administered to a pregnant woman. Small amounts of finasteride have been recovered from the semen in treated subjects. 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. Therefore, when the patient's sexual partner is or may become pregnant, the patient should either avoid exposure of his partner to semen (e.g. by use of a condom) or discontinue treatment with finasteride.

Exposure to finasteride - risk to male fetus

Women who are or may become pregnant should not handle crushed or broken Finasteride 1 mg Film-coated Tablets because of the possibility of absorption of finasteride and the risk to a male fetus (see above and section 6.6).

Lactation

Finasteride 1mg Film-coated Tablets are not indicated for use in women. It is not known whether it is excreted in human milk.

4.7 Effects on ability to drive and use machines

Finasteride has a negligible influence on the ability to drive and use machines.

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 ($\geq 1/10$); Common ($\geq 1/100, 1/10$); Uncommon ($\geq 1/1,000, < 1/100$); Rare ($\geq 1/10,000, 1/1,000$); 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.

Immune system disorders:	<i>Not known:</i> Hypersensitivity reactions, including rash, pruritus, urticaria and swelling of the lips and face.
Cardiac disorder:	<i>Not known:</i> Palpitation
Psychiatric:	<i>Uncommon*:</i> Decreased libido.
Hepatobiliary disorders:	<i>Not known:</i> Increased hepatic enzymes.
Reproductive system and breast disorders	<i>Uncommon*:</i> Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate).
	<i>Not known:</i> Breast tenderness and enlargement, Testicular pain, infertility**. **See section 4.4.

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

Drug-related sexual 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.

Persistence of erectile dysfunction after discontinuation of treatment with PROPECIA has been reported in post-marketing use.

4.9 Overdose

Patients have received single doses of finasteride up to 400mg and multiple doses up to 80mg/day without adverse effects. There is no specific recommended treatment of overdose of finasteride.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations

ATC code: D11AX10

Finasteride is a synthetic 4-azasteroid and is chemically similar to testosterone and acts as a competitive and specific inhibitor of steroid 5 α -reductase type II, an intracellular enzyme that converts testosterone into the more potent androgen 5 α -dihydrotestosterone (DHT). Finasteride has no affinity for the androgen receptor and has no androgenic, anti-androgenic, oestrogenic, anti-oestrogenic, or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching significant suppression within 24 hours of dosing.

Hair follicles contain type II 5 α -reductase. In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT. Administration of finasteride decreases scalp and serum DHT concentrations in these men. Men with a genetic deficiency of type II 5 α -reductase do not suffer from male pattern hair loss. Finasteride inhibits a process responsible for miniaturisation of the scalp hair follicles, which can lead to reversal of the balding process.

Clinical studies in men with mild to moderate, but not complete, vertex hair loss and/or frontal/mid-area hair loss demonstrated that: treatment with finasteride for 5yr reduced androgenetic alopecia compared to both baseline and placebo as early as 3 months, and promoted hair growth at 6 months (the earliest time point assessed); maximal efficacy was observed after treatment for 2 years.

Therefore, finasteride stabilised hair loss compared with placebo treatment in men with androgenetic alopecia. An additional placebo-controlled study over a 48-week period found that finasteride promoted the conversion of hair follicles into the actively growing hair phase.

A study conducted in post-menopausal women with androgenetic alopecia showed that finasteride was ineffective compared with placebo over a 12-month period.

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 liters (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 finasteride. Studies in rhesus monkeys showed that this amount is not considered to constitute a risk to the developing male fetus (see 4.6 Pregnancy and lactation, and 5.3 Preclinical safety data).

Biotransformation:

Finasteride is metabolized primarily via but does not affect the cytochrome P450 3A4 system. Following an oral dose of ¹⁴C-finasteride in man, two metabolites of finasteride were identified that possess only a small fraction of the 5-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 feces. 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 healthy volunteers.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of general toxicity, genotoxicity and carcinogenicity.

Reproduction toxicity studies:

Dose-dependent development of hypospadias was 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.

Intravenous administration of finasteride to pregnant rhesus monkeys at doses as high as >800 ng/day during the entire period of embryonic and fetal development resulted in no abnormalities in male fetuses. This represents at least 750 times the highest estimated exposure of pregnant women to finasteride from semen. In confirmation of the relevance of the Rhesus model for human fetal development, oral administration of finasteride 2mg/kg/day (100 times the recommended human dose or approximately 12 million times the highest estimated exposure to finasteride from semen) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**Tablet core:

Lactose monohydrate
Cellulose, Microcrystalline (E460)
Pregelatinised Maize Starch
Sodium Starch Glycolate (Type A)
Docusate Sodium
Magnesium Stearate (E470b)

Tablet coating:

Red and yellow iron oxides (E172)
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special requirements.

6.5 Nature and contents of container

Aluminium foil/PVC/PE/PVdC blisters in cartons of 14, 28 or 98 tablets.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Crushed or broken tablets of Finasteride 1mg Film-coated Tablets 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 4.6 Pregnancy and lactation).

Finasteride tablets have a film coating which prevents contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

7 MARKETING AUTHORISATION HOLDER

Dr. Reddy's Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD, UK
Tel: +44 (0) 1482 860228
Fax: +44 (0) 1482 872042

8 MARKETING AUTHORISATION NUMBER(S)

PL 08553/0251

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/07/2009

10 DATE OF REVISION OF THE TEXT

15/07/2009

Module 3

Product Information Leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER Finasteride 1mg Film-coated Tablets

Read all of this leaflet carefully before you start taking this medicine:

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

1. What Finasteride 1mg Tablets are and what they are used for

Your doctor has prescribed these tablets because you have the early stages of male hair loss, which is also known as androgenetic alopecia (AGA). Finasteride 1mg Tablets are used to prevent hair loss and to encourage hair growth in men.

The active substance (which makes this medicine work) is finasteride. Finasteride is a type of medicine called a 5-alpha-reductase inhibitor.

2. Before you take Finasteride 1mg Tablets

Do not take Finasteride 1mg Tablets if you

- are allergic to finasteride or any of the other ingredients in these tablets, listed in Section 6.
- are a woman, a child or adolescent.
- are taking Finasteride 5mg Tablets or any other medicine to shrink an enlarged prostate.

Check with your doctor before taking Finasteride 1mg tablets

- if you have a lot of difficulty passing urine (water)
- if you suffer from liver problems
- Finasteride can affect a blood test called PSA. If you need a PSA test, you should tell the doctor that you are taking finasteride.

Taking other medicines

Finasteride 1mg Tablets do not usually interfere with other medicines. However you should tell your doctor or pharmacist about any other medicines that you are taking, including any you have bought without a prescription.

Pregnancy

Women must not use Finasteride Tablets.

Finasteride can pass through the skin, therefore the tablets are film coated to prevent contact with finasteride. Women who are or might become pregnant should not handle crushed or broken Finasteride tablets. If finasteride is absorbed through the skin by a woman who is pregnant with a male foetus, the normal development of the baby's sex organs may be affected.

If your sexual partner is or could be pregnant, you must avoid exposing her to your semen, which could contain a small amount of finasteride – for example by using a condom during sexual activity.

If you think a pregnant woman has come into contact with finasteride, you should consult a doctor.

Driving and using machines

Driving and using machinery is not known to be affected by this medicine.

Sugar content

This medicine contains a type of sugar called lactose, so if your doctor has told you that you have an intolerance to sugars, do not take the tablets.

3. How to take Finasteride 1mg Tablets

Finasteride 1mg Tablets are for oral use and are for men only.

Always take your medicine exactly as your doctor has told you and according to the instructions printed on the label of the pack. If you are not sure, check with your doctor or pharmacist.

Adults: The usual dose is **one tablet every day** with or without food.
The tablets should be **swallowed whole and must not be crushed or divided.**

Children: Finasteride 1mg Tablets **must not be used** in children.

Elderly patients or those with kidney disorders: Usually no dose adjustment is needed and the same dose as for other adults should be used.

If you take more Finasteride 1mg Tablets than you should

If you take more than the recommended number of tablets, contact your doctor or pharmacist for advice straight away. No side effects have been reported under these circumstances.

If you forget to take Finasteride 1mg Tablets

Take the forgotten tablet when you remember, then take your next tablet as usual the following day.
Do not take a double dose to make up for the missed dose.

Length of treatment

Generally it takes three to six months of treatment before you will stop losing your hair. Continued treatment is required to prevent hair loss from returning. If you stop treatment, hair loss will return after 6 months and will be as it was before by 9-12 months.

4. Possible side effects

Like all medicines, Finasteride 1mg Tablets can cause side effects, although not everybody gets them.

Uncommon: (occurs in more than 1 in 1,000 but less than 1 in 100 patients): Reduced desire to have sex, difficulty having an erection, ejaculation problems such as a decreased amount of semen.

Frequency unknown: fast heart beat, tenderness and enlargement of the male breasts, difficulty having erection after stopping treatment, swelling or pain in the testicles, elevated liver enzymes and allergic reactions such as skin rashes, itching, hives or swelling of the face and lips. Taking Finasteride 1mg Tablets for a long time may increase your risk of infertility.

If you have any of these side effects, they get worse or if you notice any side effects not listed, please tell your doctor or pharmacist.

5. How to store

Keep your Finasteride 1mg Tablets in a safe place out of the reach and sight of children.

Do not take this medicine after the expiry date which is stated on the blister.

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

Each tablet contains 1mg of the active ingredient finasteride. The other ingredients are lactose monohydrate, cellulose microcrystalline (E460), starch pregelatinised, sodium starch glycolate (Type A), magnesium stearate (E470b), docusate sodium, hypromellose (E464), titanium dioxide (E171), macrogol and red and yellow iron oxides (E172). The sodium content of each tablet is 3.85mg.

Finasteride 1mg Tablets are light-brown, film-coated tablets with the following markings: 'FIN' on one side and '1' on the other side. The tablets are in blister packs containing 14, 28 or 98 tablets.

Marketing Authorisation Holder and Manufacturer (also EU batch release site)

Dr Reddy's Laboratories (UK) Ltd, 6 Riverview Road, Beverley, HU17 0LD, UK
Tel: +44 (0) 1482 860228; Fax: +44 (0) 1482 872042

This medicine is authorised in Member States of the EEA under the following names:

UK: Finasteride 1mg film-coated Tablets (PL 08553/0251)

Spain: Finasterida 1mg Aphar Comprimidos Recubiertos EFG

Italy: Finasteride Reddy's 1mg compresse rivestite con film

Bulgaria: ENYDE 1mg, филмирана таблетка Romania: ENYDE 1mg, comprimate filmat

This leaflet was last approved on 07/2009 Component code: © Dr. Reddy's Laboratories (UK) Ltd

Module 4 Labelling

BN: 0000

Finasteride 1mg Film-coated Tablets
Dr Reddy's Laboratories (UK) Ltd

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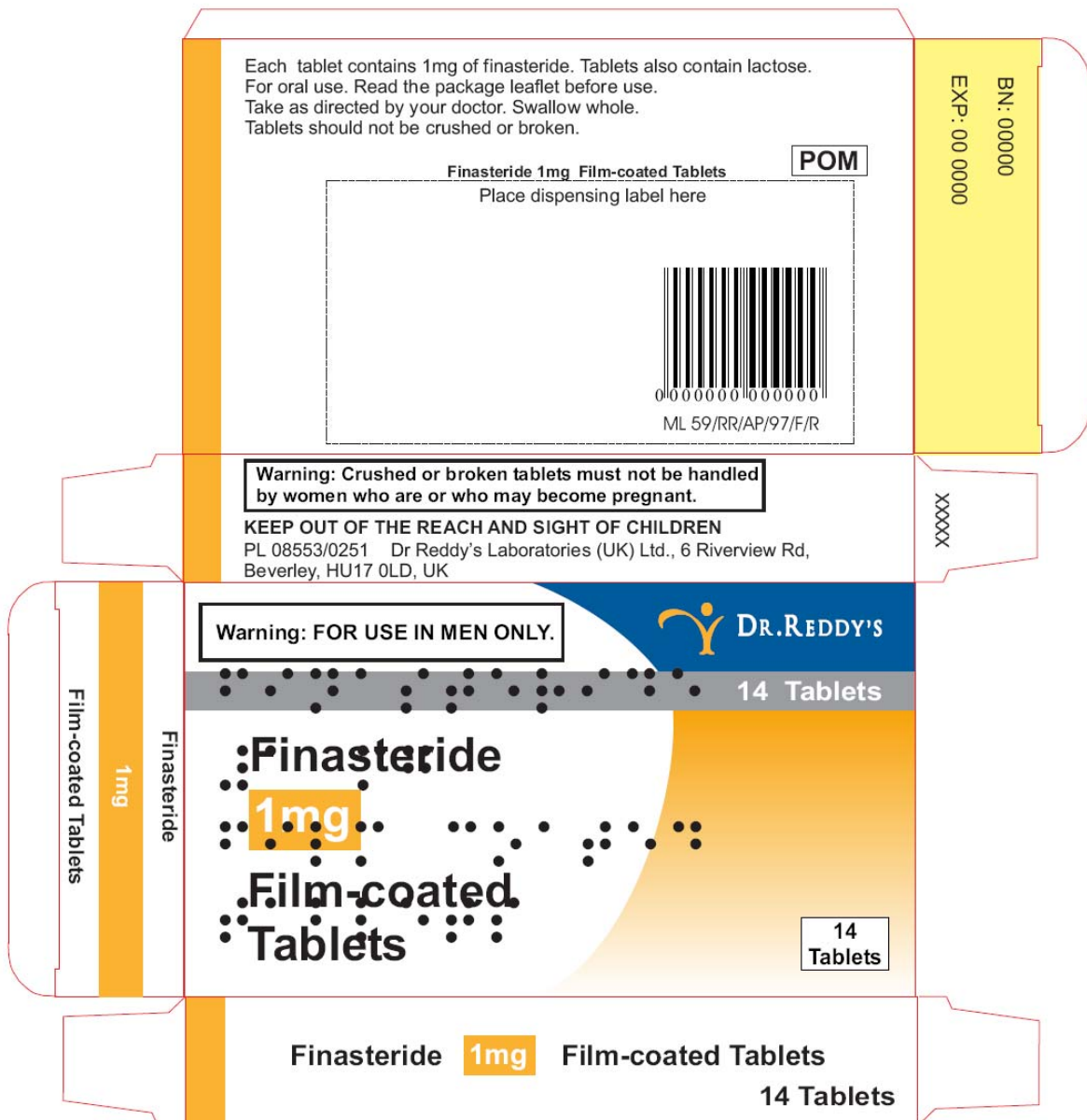
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Dr Reddy's Laboratories (UK) Ltd

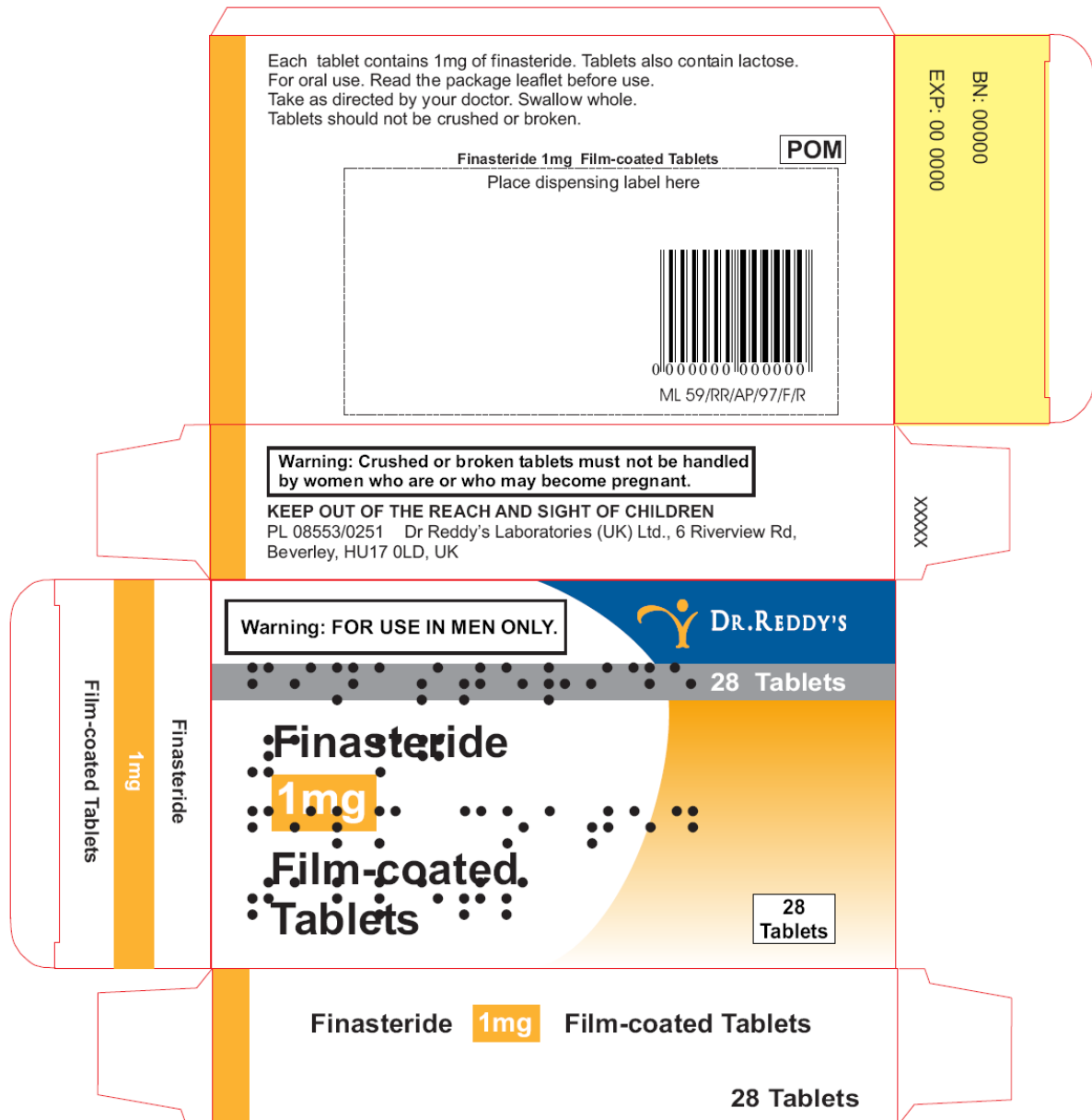
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Dr Reddy's Laboratories (UK) Ltd

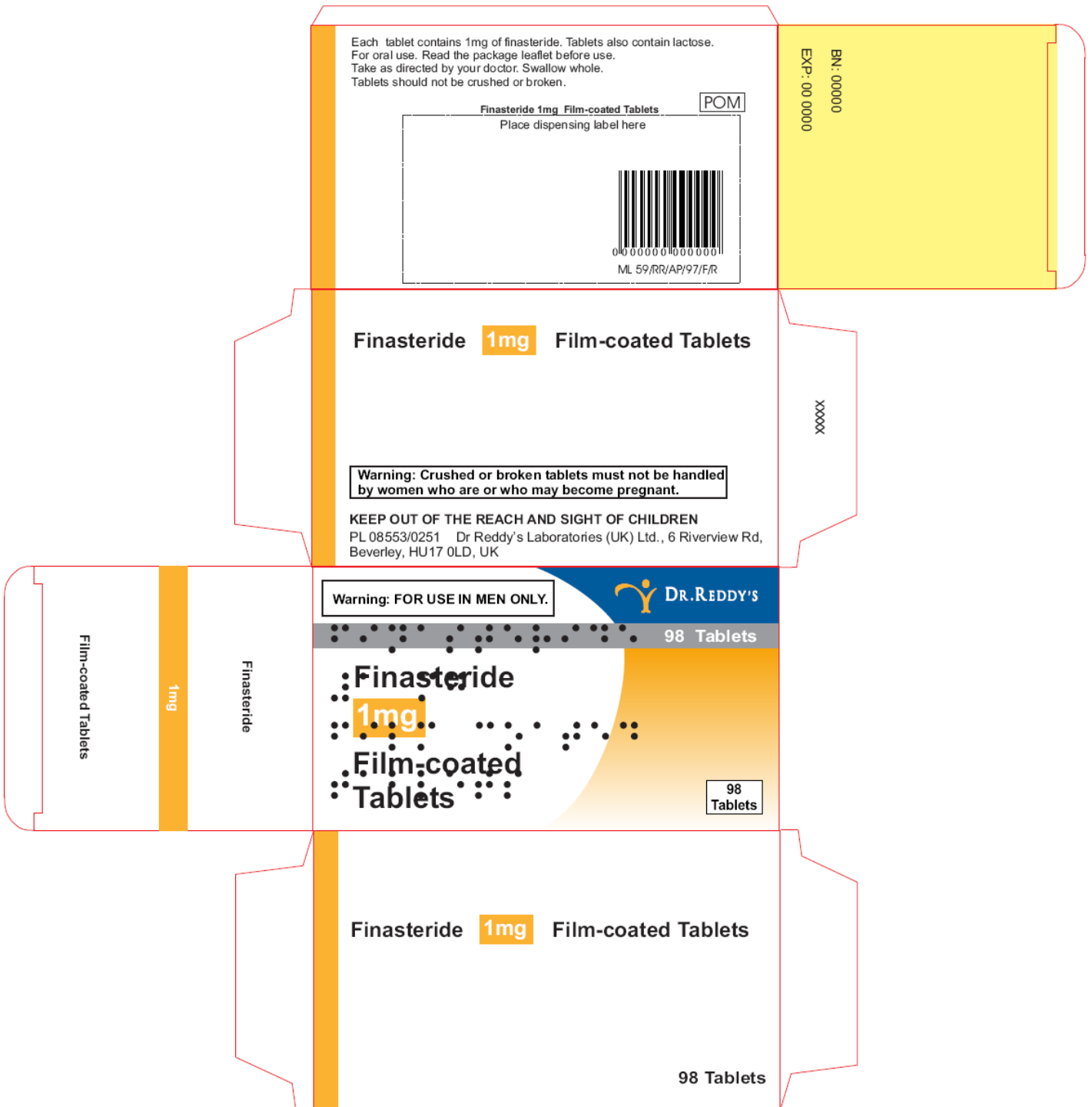
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Dr Reddy's Laboratories (UK) Ltd

Finasteride 1mg Film-coated Tablets
Dr Reddy's Laboratories (UK) Ltd

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Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Bulgaria, Italy, Romania, Spain and the UK considered that the application for Finasteride 1mg film-coated Tablets could be approved. This product is a prescription only medicine (POM) for the treatment of hair loss in the early stages of androgenetic alopecia in men. Finasteride 1mg film-coated Tablets stabilizes the process of androgenetic alopecia in men 18-41 years of age.

This application for Finasteride 1mg film-coated Tablets is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Proscar 5mg Film-Coated Tablets, which was originally approved in the UK to Merck Sharpe Dohme Limited on 27th May 1992.

Finasteride is a testosterone-5-alpha reductase inhibitor. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone. Finasteride is indicated for the treatment of men with male pattern hair loss and for the treatment and control of benign prostatic hyperplasia.

No new preclinical studies were conducted, which is acceptable given that the products contain 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.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Finasteride 1mg film-coated Tablets
Name(s) of the active substance(s) (INN)	Finasteride
Pharmacotherapeutic classification (ATC code)	Other dermatological preparations (D11AX10)
Pharmaceutical form and strength(s)	1mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1279/001/DC
Reference Member State	United Kingdom
Member States concerned	Bulgaria, Italy, Romania and Spain
Marketing Authorisation Number(s)	PL 08553/0251
Name and address of the authorisation holder	Dr. Reddy's Laboratories (UK) Limited 6 Riverview Road Beverley HU17 0LD, United Kingdom

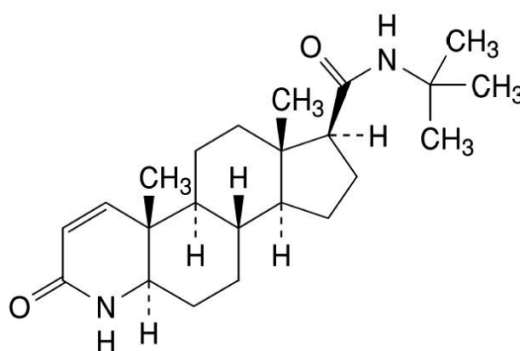
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

- INN: Finasteride
- Chemical name: (1) *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide (Ph Eur name)
- (2) *N*-tert-Butyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide
- (3) (5 α -17 β)-*N*-(1,1-Dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide
- (4) 17- β -(*N*-tert-butylcarbonyl)-4-aza-5 α -androst-1-en-3-one

Structural formula:



- Molecular formula: C₂₃H₃₆N₂O₂
- 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 is the subject of a European Pharmacopoeia monograph.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance finasteride.

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.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active finasteride, 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.

Satisfactory specifications and certificates of analysis have been provided 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 proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

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

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients lactose monohydrate, cellulose, microcrystalline (E460), pregelatinised maize starch, sodium starch glycolate (Type A), docusate sodium, magnesium stearate (E470b). All the ingredients within the body of the capsule comply with their relevant European Pharmacopoeia monographs.

The capsule shell contains: red and yellow iron oxides (E172), hypromellose (E464), titanium dioxide (E171), macrogol. All excipients within the tablet coating comply with in-house specifications.

None of the excipients with the exception of lactose monohydrate contain material of animal or human origin. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption.

The applicant had provided an assurance that the magnesium stearate is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Proscar 5mg Film-Coated Tablets (Merck Sharpe Dohme Limited).

With the exception of the excipients, the reference product used in the bioequivalence study is qualitatively and quantitatively identical to the reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Proscar 5mg Film-Coated Tablets (Merck Sharpe Dohme Limited).

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator product.

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on two pilot-scale batches and a production-scale batch of finished product and the results appear satisfactory. The applicant has committed to perform process validation on future production-scale batches.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in blister packs consisting of aluminium foil, polyvinyl chloride (PVC), polyethylene (PE) and polyvinylidene chloride (PVdC).

The product is packaged in sizes of 14, 28 and 98 tablets.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on three batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of three years, with no specific storage instructions.

Suitable post approval stability commitments have been provided to follow-up the batches from the current studies and to place future commercial-scale batches on stability.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

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

The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS

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 has provided none. The applicant's non-clinical overview is satisfactory, providing an appropriate review of the drug's pharmacology and toxicology.

III.3 CLINICAL ASPECTS

1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports

To support this application, the marketing authorisation holder has submitted one single dose bioequivalence study.

A randomised, open-label, 2-treatment, 2-sequence, 2-period, crossover, single dose bioequivalence study of Finasteride 1mg Tablet (Test) and Propecia (finasteride) 1mg Tablet (Reference) in healthy, adult, human male subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed pre- and at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 16, 24 and 36 hours post dose in each treatment period. There was a washout period of 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

Treatment	AUC _{0-t} (ng/ml/h)	AUC _{0-∞} (ng/ml/h)	C _{max} (ng/ml)
Finasteride:			
Test	236.6449	247.2444	37.7099
Reference	254.3683	267.3247	40.0795
Ratio (90% CI)	93.03 (87.83 to 98.54%)	92.49 (86.59 to 98.79%)	94.09 (88.77 to 99.72%)

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for finasteride lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

Efficacy

No new data on the efficacy of finasteride are submitted and none are required for this type of application.

Safety

No new safety concerns were raised from the adverse events occurring in the bioequivalence study. No other new safety data were submitted with this application and none were required.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPC is consistent with that for the originator product.

Conclusion

The grant of a marketing authorisation is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY**

The important quality characteristics of Finasteride 1mg 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 an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Finasteride 1mg film-coated Tablets and the originator product Proscar 5mg Film-Coated Tablets (Merck Sharpe Dohme Limited).

No new or unexpected safety concerns arise from this application.

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

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with finasteride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome