

Public Assessment Report

Decentralised Procedure

Finasteride 5mg Tablets
Finasteride

UK/H/989/01/DC

UK licence no: PL 08553/0261

Applicant: Dr Reddy's Laboratories (UK) Ltd

LAY SUMMARY

The MHRA granted Dr Reddy's Laboratories Ltd Marketing Authorisation (licence) for the medicinal product Finasteride 5mg Tablets (PL 08553/0261) on 5th June 2007. This is a prescription-only medicine (POM) used only in men for the treatment and control of Benign Prostatic Hyperplasia (BPH).

This is a Decentralised application for Finasteride 5mg Film-Coated Tablets submitted under Article 10.1 of Directive 2001/83, claiming to be a generic medicinal product of Proscar 5mg tablets (PL 00025/0279) licensed to Merck, Sharp and Dohme in May 1992.

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

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

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Module 1

Product Name	Finasteride 5mg Tablets
Type of Application	Generic, Article 10.1
Active Substance	Finasteride
Form	Tablets
Strength	5mg Tablets
MA Holder	Dr Reddy's Laboratories (UK Limited)
RMS	UK
CMS	ES
Procedure Number	UK/H/989/01/DC
Timetable	Day 120– 8 th May 2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Finasteride 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Excipient(s):

Each tablet also contains 83.5mg of lactose and 6.6mg of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Blue, oval biconvex tablets marked with 'FIN' on one side and '5' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Finasteride is ONLY indicated for use in men for the treatment and control of Benign Prostatic Hyperplasia (BPH). Finasteride causes regression of the enlarged prostate, improves urinary flow and symptoms of BPH. Finasteride reduces the risk of acute urinary retention and the need for surgery including prostatectomy and transurethral resection of the prostate.

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

4.2 Posology and method of administration

Oral use.

The recommended daily dose is one 5mg tablet, which may be taken with or without food. The tablets should be swallowed whole and must not be divided or crushed (see section 6.6). Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1). Early symptomatic improvement may be observed, but treatment for at least 6 months may be necessary to assess whether a therapeutic response has been achieved.

Dosage in the elderly. No dosage adjustment is required in the elderly although pharmacokinetic studies have shown that the elimination rate of finasteride is slightly decreased in patients over the age of 70 (see section 5.2).

Dosage in renal insufficiency. Dosage adjustments are not necessary in patients with varying degrees of impaired renal function (creatinine clearance as low as 9ml/min) as in the pharmacokinetic studies renal insufficiency was not found to affect elimination of finasteride. Finasteride has not been studied in patients on haemodialysis (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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Finasteride is contra-indicated in women who are or may potentially become pregnant (see section 4.4, 4.6 and 6.6).

Finasteride is not indicated in either women or children.

4.4 Special warnings and precautions for use

General

- Patients with a large residual volume of urine and/or severely diminished urinary flow should be carefully monitored due to the risk of obstructive uropathy.

- Consultation with a urologist should be considered in patients treated with finasteride.

- Obstruction due to trilobular growth pattern of the prostate should be excluded before starting treatment with finasteride.

- There is no experience in patients with liver insufficiency. Caution is advised in patients with decreased hepatic function as the plasma-levels of finasteride may be increased in such patients.

- Since finasteride inhibits the conversion of testosterone to dihydrotestosterone, it can inhibit the development of the external genitalia of the foetus if it is given to a woman carrying a male fetus (see section 5.3 and 6.6).
- 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).

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

No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride. In clinical studies, serum PSA levels and prostate biopsy was determined in patients with BPH. Digital rectal examination, and if necessary determination of prostate-specific-antigen (PSA) in serum should be carried-out in patients with BPH before initiating finasteride therapy and periodically throughout treatment to rule-out prostate cancer. Generally, baseline PSA levels of >10ng/ml (Hybritech) prompts further evaluation and consideration for a biopsy. Further evaluation is advisable for PSA levels of between 4 and 10ng/ml. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal range do not rule out prostate cancer regardless of treatment with finasteride. PSA levels of <4ng/ml does not rule out prostate cancer.

Finasteride causes a decrease in plasma 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 a product containing 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 levels, although it may vary in individual patients. An analysis of PSA values in more than 3,000 patients in a 4-year study with a product containing finasteride confirmed that, in typical patients treated with a product containing finasteride for a period of 6 months or more, PSA values should be doubled for comparison with normal levels in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increase in PSA levels of patients treated with finasteride should be carefully evaluated, including consideration of non-compliance with finasteride treatment. Percent of 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.

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 system. 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.

Laboratory findings. Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels fall in patients treated with a product containing finasteride. In most patients, a rapid decrease in PSA is observed during the first month of therapy, after which time PSA levels stabilise to a new level. The post-treatment level is approximately half the pre-treatment value. Therefore, in typical patients treated with a product containing finasteride for a period of 6 months and more, PSA values should be doubled for comparison with normal ranges in untreated men (see section 4.4).

4.6 Pregnancy and lactation

Finasteride is contraindicated in women (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 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. The genetic and epigenetic effects of finasteride treatment on sperm are unknown. 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 tablets of Finasteride 5mg tablets because of the possibility of absorption of finasteride and the risk to a male fetus (see section 6.6).

Lactation

Finasteride 5mg 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

Undesirable effects are classified according to their frequency:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $<1/10$); Uncommon ($\geq 1/1,000$ to $\leq 1/100$); Rare ($\geq 1/10,000$ to $\leq 1/1,000$); Very rare ($\leq 1/10,000$ including isolated reports).

The most commonly reported adverse drug reactions are impotence, decreased libido, ejaculation disorder, decreased volume of ejaculate; breast enlargement, breast tenderness and rash, which occur in less than 10% of patients treated with finasteride. The length of treatment with finasteride is not associated with a greater number of adverse events. The incidence of new drug-related sexual adverse experiences decreases with the duration of treatment.

The following undesirable effects have been reported during the first year of clinical trials and/or post-marketing:

Reproductive system and breast disorders

Common ($\geq 1/100$, $<1/10$): decreased volume of ejaculate, impotence, reduced libido.

Uncommon ($\geq 1/1000$, $<1/100$): ejaculation disorder, breast enlargement and tenderness.

Rare ($\geq 1/10,000$, $<1/1000$): testicular pain.

Very rare ($<1/10,000$) including isolated reports: breast secretion, breast nodules (requiring surgical removal) in isolated patients

Skin and subcutaneous tissue disorders

Uncommon ($\geq 1/1000$, $<1/100$): rash.

Immune system disorders

Rare ($\geq 1/10,000$, $<1/1000$): hypersensitivity reactions, including pruritus, urticaria, and oedema of lips and face.

In the 2nd to 4th year of the 4-year placebo-controlled PLESS trial with 3,040 men and in follow-up studies lasting five years (including 853 patients treated for 5–6 years) no significant differences between the treatment groups were found in terms of impotence, decreased libido and ejaculation disorder; and the frequency of new sexual undesirable effects associated with the medicinal product decreased as treatment continued. Breast enlargement and tenderness were more common in the 2nd to 4th year of the PLESS trial but their frequency remained below 2% in both cases. The frequency of rash did not change.

Medical Therapy for Prostatic Symptoms (MTOPS)

The MTOPS study compared finasteride 5 mg/day (n = 768), doxazosin 4 or 8 mg/day (n = 756), combined treatment with finasteride 5 mg/day and doxazosin 4 or 8mg/day (n = 786) and placebo (n = 737). In this study, the safety and tolerability profile of combined therapy was generally similar to that of each of the medicinal products used separately. However, undesirable effects associated with the “nervous system” and “genitourinary system” organ classes were observed more frequently when the two medicinal products were combined (see table overleaf).

	Placebo (%)	Doxazosin* (%)	Finasteride** (%)	Finasteride** + doxazosin* (%)
One or more undesirable effects	46.4	64.9	52.5	73.8
General signs:	11.7	21.4	11.6	21.5

Asthenia	7.1	15.7	5.3	16.8
Cardiovascular disorders:	10.4	23.1	12.6	22.0
Hypotension***	0.7	3.4	1.2	1.5
Postural hypotension	8.0	16.7	9.1	17.8
Nervous system disorders:	16.1	28.4	19.7	36.3
Dizziness	8.1	17.7	7.4	23.2
Loss of libido	5.7	7.0	10.0	11.6
Drowsiness	1.5	3.7	1.7	3.1
Genitourinary disorders:	18.6	22.1	29.7	36.8
Ejaculation disorders	2.3	4.5	7.2	14.1
Gynaecomastia	0.7	1.1	2.2	1.5
Impotence	12.2	14.4	18.5	22.6
Other types of sexual dysfunction	0.9	2.0	2.5	3.1

*doxazosin: 4 to 8mg/day

**finasteride: 5mg/day

***other than postural hypotension

Other long-term results. In a 7-year placebo-controlled clinical trial, the results of a prostatic needle biopsy were available for analysis in 9,060 of the 18,882 healthy men who participated in the study. Prostate cancer was diagnosed in 803 (18.4%) of finasteride-treated men versus 1147 (24.4%) of men who received placebo, of which 280 (6.4%) versus 237 men (5.1%), respectively had a Gleason score of 7–10. Approximately, 98% of cases of prostate cancer in this trial were classified as intracapsular (stage T1 or T2). The relationship between long-term use of finasteride and tumours with a Gleason's score of 7–10 is unknown.

Laboratory test findings: When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with finasteride. In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates to 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.

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. No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: testosterone 5-alpha reductase inhibitor.

ATC code: G04C B01

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). The prostate gland and, consequently, also the hyperplastic prostate tissue are dependent on the conversion of testosterone to DHT for their normal function and growth. DHT causes enlargement of the prostate gland leading to benign prostatic hyperplasia. *In vitro* studies using human 5 α -reductase demonstrate that inhibition

occurs without affecting the binding of testosterone or DHT to the androgen receptor. Finasteride in itself possesses no androgenic, anti-androgenic, or other steroid or hormone-related properties. Clinical studies show a rapid reduction in the serum DHT levels of 70%, which leads to a reduction in prostate volume. After 3 months, a reduction of approximately 20% in volume of the gland occurs, and the shrinking continues and reaches approximately 27% after 3 years. Marked reduction takes place in the periurethral zone immediately surrounding the urethra. Urodynamic measurements have also confirmed a significant reduction of detrusor pressure as a result of the reduced obstruction. Significant improvements in maximum urinary flow rate and symptoms have been obtained after a few weeks, compared with the start of treatment. Differences from placebo have been documented at 4 and 7 months, respectively.

All efficacy parameters have been maintained over a 3-year follow-up period.

Effects of four years' treatment with finasteride on incidence of acute urinary retention, need for surgery, symptom-score and prostate volume:

In clinical studies of patients with moderate to severe symptoms of BPH, an enlarged prostate on digital rectal examination and low residual urinary volumes, finasteride reduced the incidence of acute retention of urine from 7/100 to 3/100 over four years and the need for surgery (TURP or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA symptom score (range 0-34), a sustained regression in prostate volume of approximately 20% and a sustained increase in urinary flow rate.

5.2 Pharmacokinetic properties

Absorption:

Finasteride is absorbed following oral administration and peak plasma concentrations are achieved in 1 to 2 hours. The mean bioavailability has been reported at both 63% and 80% and is unaffected by food. Peak plasma concentrations are reached approx. 2 hours after drug intake, and absorption is complete after 6-8 hours.

Distribution:

Finasteride is about 90% bound to plasma protein. Clearance and volume of distribution are approx. 165 ml/min (70-279 ml/min) and 76 l (44-96 l), respectively. Accumulation of small amounts of finasteride is seen on repeated administration. After a daily dose of 5 mg the lowest steady-state concentration of finasteride has been calculated to be 8-10 ng/ml, which remains stable over time. Finasteride has been found to cross the blood-brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients (see section 4.6).

Biotransformation:

Finasteride is metabolised in the liver and excreted in the urine and faeces as metabolites. Finasteride does not significantly affect the cytochrome P 450 enzyme system. Two metabolites with low 5 α -reductase-inhibiting effects have been identified.

Elimination:

Mean half-life is 6 hours (range 4-12 hours) in patients under 60 years of age but may be prolonged to about 8 hours (range 6-15 hours) in those 70 years of age or older. This is of no clinical significance and does not warrant a reduction in dosage.

In patients with chronic renal impairment, whose creatinine clearance ranged from 9 to 55 ml/min, the disposition of a single dose of radiolabeled-finasteride was no different from that in healthy volunteers (see section 4.2). Protein binding also did not differ in patients with renal impairment. A proportion of the metabolites, which are normally excreted renally, were 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 (see section 4.2). Finasteride has been found to cross the blood-brain barrier.

5.3 Preclinical safety data

Studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans in excess of those already listed in other sections of the SPC.

Reproduction toxicity studies:

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

The changes described above are expected pharmacological effects of Type-II-5 α -reductase-inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed in utero to finasteride are similar to those reported in male infants with a genetic deficiency of Type-II-5 α -reductase. It is for these reasons that finasteride is contraindicated in women who are or may potentially be pregnant. No effects were seen in female offspring exposed in utero to any dose of finasteride. No studies have investigated the potential effects of finasteride in semen coming into direct contact with a fertilised egg, embryo and fetus. 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:

Indigo Carmine (E132)
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Keep blister in the outer carton.

6.5 Nature and contents of container

Blister strips made of PVC/PE/PVdC or cold formable foil bases and lidded with aluminium foil. Available pack sizes are: 28, 30, 50 and 100 tablets, although not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements and not via waste water or household waste. Pharmacists can advise of safe disposal to protect the environment.

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

7 MARKETING AUTHORISATION HOLDER

Dr Reddy's Laboratories (UK) Ltd,
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- 8 MARKETING AUTHORISATION NUMBER(S)**
PL08553/0261
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
05/06/2007
- 10 DATE OF REVISION OF THE TEXT**
05/06/2007

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Finasteride 5mg Tablets

Read all 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What are Finasteride 5mg Tablets and what are they used for
2. Before you take Finasteride 5mg Tablets
3. How to take Finasteride 5mg Tablets
4. Possible side effects
5. How to store Finasteride 5mg Tablets
6. Further information

1. What Are Finasteride 5mg Tablets And What They Are Used For

The name of this medicine is Finasteride 5mg Tablets (also referred to as finasteride in this leaflet). Finasteride 5mg Tablets are blue, oval, film-coated tablets with the following markings: 'FIN' on one side and '5' on the other side. The tablets are presented in blister strips containing 28, 30, 50 or 100 tablets. Not all pack sizes may be marketed.

The active substance in your medicine is finasteride. Your medicine also contains lactose monohydrate, cellulose microcrystalline (E460), starch pregelatinised, sodium starch glycolate (Type A), magnesium stearate (E470b), docusate sodium. The coating of these tablets contains hypromellose (E464), titanium dioxide (E171), macrogol and indigo carmine (E132). The sodium content of each tablet is 6.6mg.

Finasteride is a type of medicine called a 5-alpha-reductase inhibitor. It is used to shrink an enlarged prostate in men. Your doctor has prescribed Finasteride 5mg Tablets for you because your prostate is bigger than normal (a condition known as Benign Prostatic Hyperplasia; BPH) which is making it more difficult for you to pass urine. Finasteride 5mg Tablets will help to reduce the risk of developing a sudden inability to pass urine, known as acute urinary retention. They will also reduce the need for prostatic surgery.

2. Before You Take Finasteride 5mg Tablets

Do not take Finasteride 5mg Tablets

- if you are allergic to any of the ingredients in these tablets, listed in Section 6.
- if you are a woman or a child. If a woman carrying a male baby comes into contact with the active ingredient, finasteride, the normal development of the baby's sex organs may be affected.

Take special care with Finasteride 5mg 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.
- Women who are pregnant or who might become pregnant should not come into contact with finasteride.
- If you have been told by your doctor that you have an intolerance to certain sugars – see below under 'Important information about some of the ingredients of Finasteride 5mg Tablets'.

If any of the above apply, you should inform your doctor before beginning treatment with Finasteride 5mg Tablets.

Taking other medicines

Finasteride 5mg Tablets do not usually interfere with other medicines, however, you should make sure you have told your doctor or pharmacist about any other medicines that you are taking, including any you have bought without a prescription.

Taking Finasteride 5mg Tablets with food and drink

Finasteride 5mg Tablets can be taken with or without food. The effectiveness of your medicine is not altered by food.

Pregnancy

Women **MUST NOT** use Finasteride Tablets. Women who are pregnant, or think they may be pregnant, should avoid any contact with finasteride, particularly if the tablets are crushed or broken.

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 a pregnant woman comes into contact with finasteride, a doctor should be consulted.

Driving and using machines

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

Important information about some of the ingredients of Finasteride 5mg Tablets

This medicine contains lactose, so patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Those patients on a sodium controlled diet should be aware that each tablet contains 6.6mg of sodium.

3. How To Take Finasteride 5mg Tablets

Finasteride 5mg 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. You should check with your doctor or pharmacist if you are not sure.

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. Finasteride 5mg Tablets may be taken on their own or with another medicine called doxazosin, which will not affect the effectiveness of your medicine. You may experience more side effects if you also take doxazosin.

Children: Finasteride 5mg Tablets MUST NOT be used in children.

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

If you take more Finasteride 5mg 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 5mg 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.

If you stop taking Finasteride 5mg Tablets

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

4. Possible side effects

Like all medicines, Finasteride 5mg Tablets can cause side effects, although not everybody gets them.

Common side-effects include: impotence (inability to maintain an erection); a reduced desire to have sex producing a reduced amount of semen

Uncommon side-effects include: Swelling and/or tenderness of the breasts; problems with ejaculation; skin rashes

Rare side-effects include: Allergic reactions including itching, hives or swelling of the face and lips; pain in the testicles

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 your Finasteride 5mg Tablets

Keep your Finasteride 5mg Tablets in a safe place out of the reach and sight of children. Do not store above 30°C and keep the blister strips in the box. 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**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

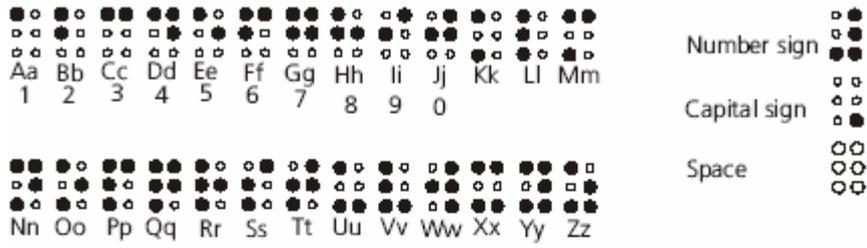
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UK: Finasteride 5mg Tablets (PL 08553/0261)

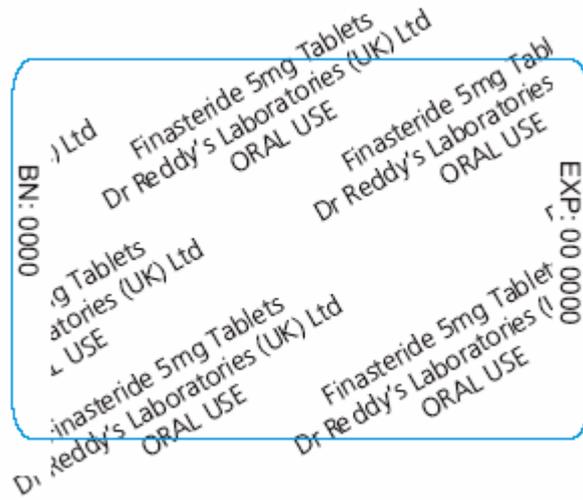
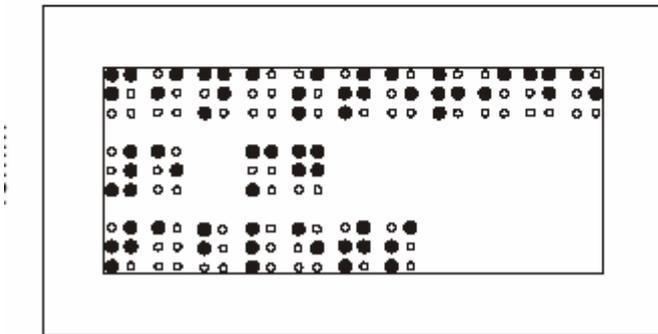
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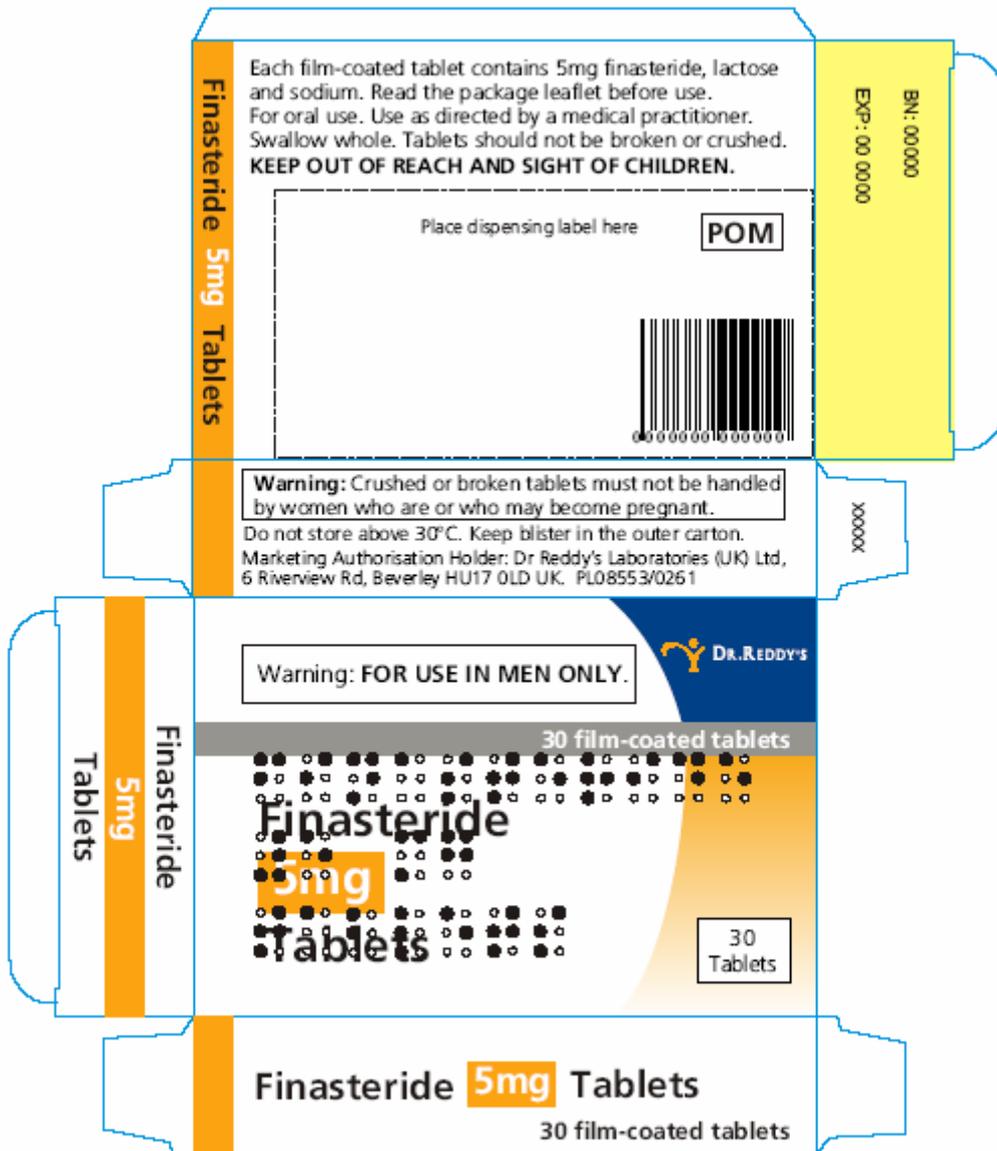
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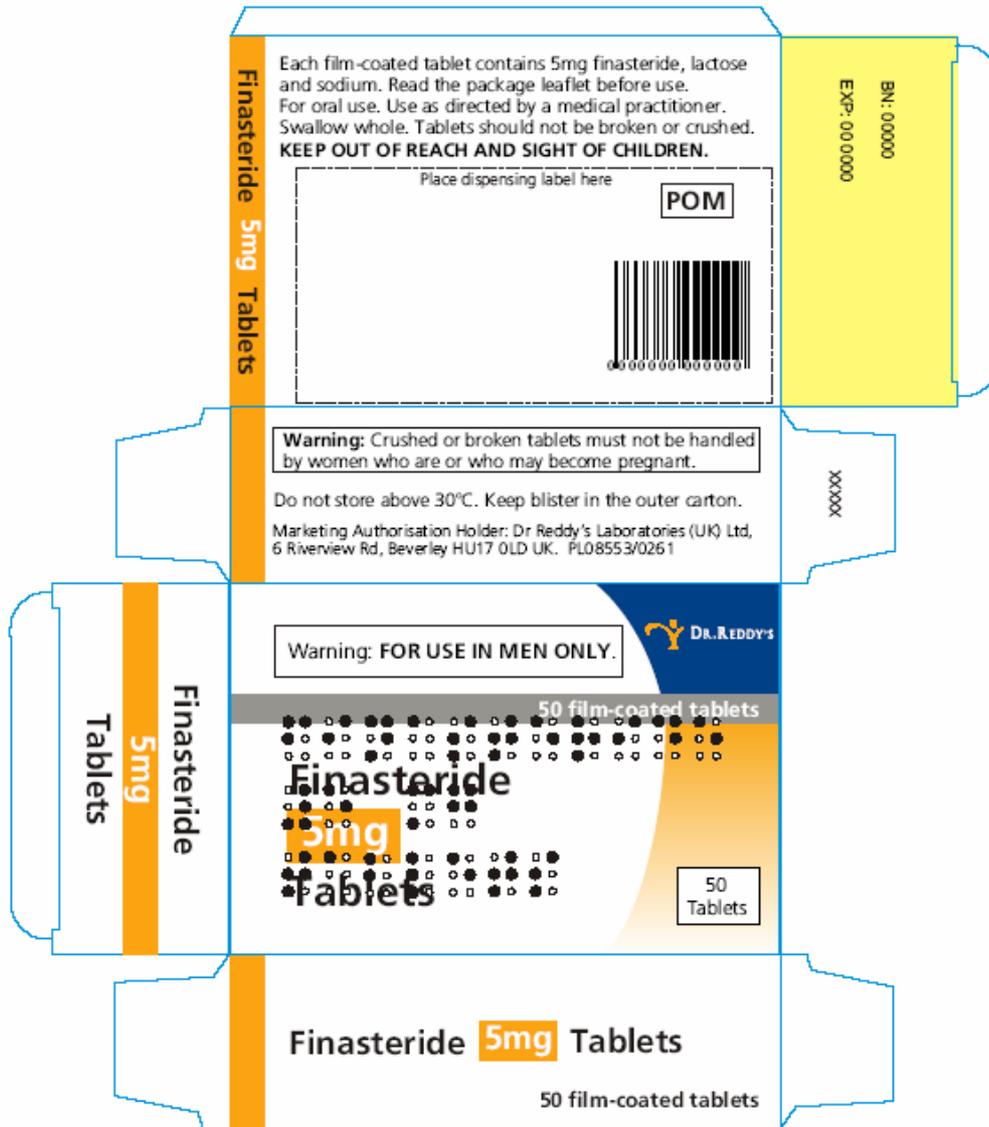
MODULE 4



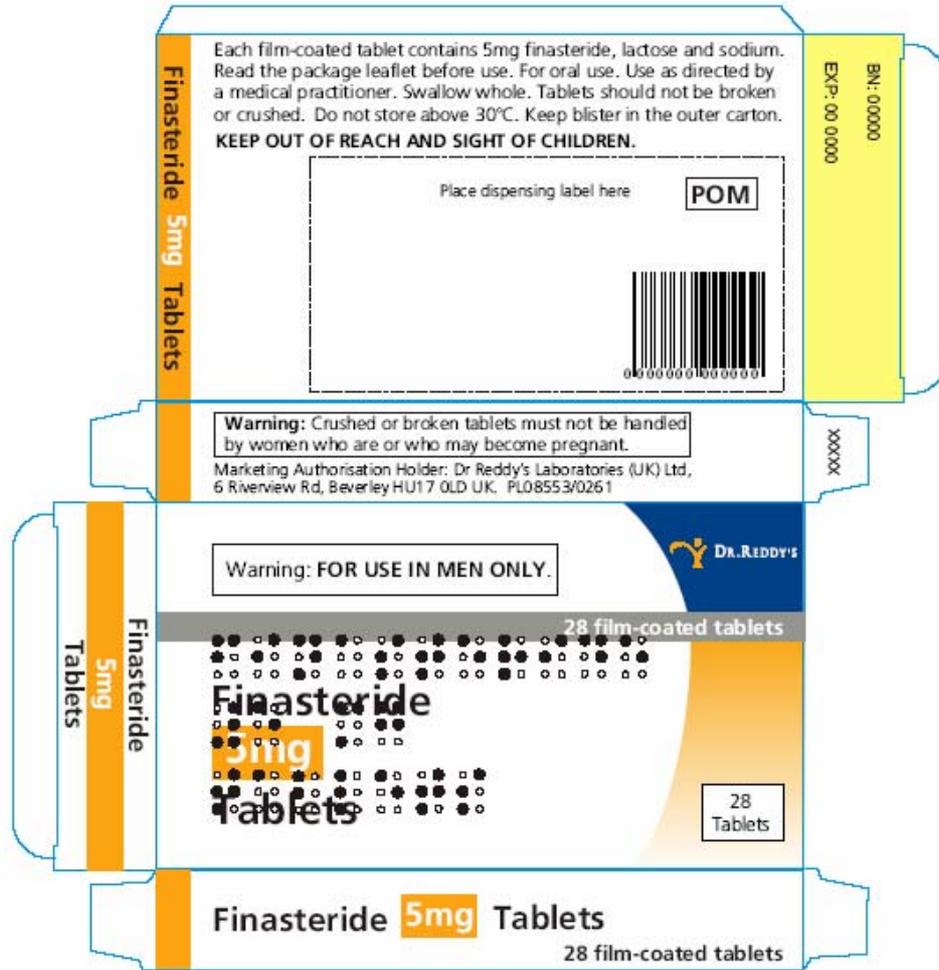
Finasteride 5mg Tablets











Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Finasteride 5mg Tablets in the treatment and control of Benign Prostatic Hyperplasia (BPH) could be approvable.

The application for Finasteride 5mg tablets is an abridged application made according to Article 10(1) of Directive 2001/83/EC submitted within the Decentralised Procedure with the UK acting as the Reference Member State (RMS). The only Concerned Member State (CMS) is Spain (ES). The reference medicinal product referred to Proscar, marketed by Merck Sharp and Dohme Ltd, was first registered in the EU (Sweden) in 1992 and was licensed in the UK in July 1997.

Finasteride is an orally active testosterone 5-alpha-reductase inhibitor and is used to treat the symptoms of benign prostatic hyperplasia (BPH) and reduce the risk of acute retention of urine and the need for surgical intervention. It acts by inhibiting the conversion of testosterone to the highly androgenic dihydrotestosterone which is thought to play a role in pathogenesis in BPH. Finasteride in itself possesses no androgenic, anti-estrogenic or other hormonal properties.

The Applicant has submitted a full study report for the pivotal study and has addressed key omissions and the RMS is now satisfied that bioequivalence between the proposed and originator (Proscar) has now been satisfactorily demonstrated.

GCP statements were provided for the bioequivalence studies.

II. ABOUT THE PRODUCT

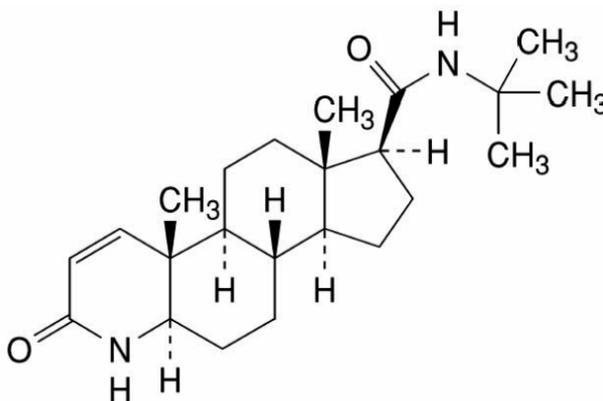
Name of the product in the Reference Member State	Finasteride 5mg Tablets
Name(s) of the active substance(s) (INN)	Finasteride
Pharmacotherapeutic classification (ATC code)	Testosterone 5 α -reductase inhibitor (GB04CB01)
Pharmaceutical form and strength(s)	5mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/989/01/DC
Reference Member State	United Kingdom
Member States Concerned	ES
Marketing Authorisation Number(s)	PL 08553/0261
Name and address of the authorisation holder	Dr Reddy's Laboratories Ltd Bachupally PO no.15, Kukatpally, Hyderabad, India

III SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug Substance

Nomenclature and structure



rINN: 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

Physical form: White or almost white, crystalline powder, practically insoluble in water, freely soluble in ethanol and methylene chloride.

Molecular formula: C₂₃H₃₆N₂O₂

Relative molecular mass: 372.6

Chirality: The molecule is chiral.

Polymorphism: Finasteride exhibits polymorphism. Based on XRD test, Dr Reddy's drug substance is Form III.

This is subject to DMF. A letter of access has been provided

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

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active finasteride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

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

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

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely cellulose, microcrystalline, docusate sodium, lactose monohydrate, magnesium stearate, pregelatinised maize starch, sodium starch glycolate, Indigo carmine (E132), titanium dioxide (E171), hypromellose, and macrogol. All excipients used comply with their respective European Pharmacopoeia monograph with the exception of Indigo carmine (E132) titanium dioxide (E171), hypromellose, and macrogol which comply with in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin are lactose monohydrate and magnesium stearate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce products containing Finasteride 5mg Tablets that are tolerable and which could be considered as generic products to the originator product Proscar 5mg Tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in to PVC/PE/Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with storage conditions of 'Do not store above 30 Degree C' and 'Keep container in the outer carton' have been set. These are acceptable.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisation should be granted for this application.

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 provides none. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. There are no objections to approval of Finasteride tablets from a non-clinical point of view.

CLINICAL ASPECTS

1. INTRODUCTION

Finasteride is ONLY indicated for use in men for the treatment and control of Benign Prostatic Hyperplasia (BPH). Finasteride causes regression of the enlarged prostate, improves urinary flow and symptoms of BPH. Finasteride reduces the risk of acute urinary retention and the need for surgery including prostatectomy and transurethral resection of the prostate.

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

This is an abridged application for a Marketing Authorisation submitted under Article 10 (1) of Directive 2001/83/EC (as amended), first paragraph so called generic application, using the decentralised procedure. The UK is RMS for the product and the CMS is ES.

This application is claiming to be a generic medicinal product of Proscar manufactured by Merck Sharpe and Dohme Limited.

2. BACKGROUND

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

3. INDICATIONS

The applicant has submitted the following:

Finasteride is ONLY indicated for use in men for the treatment and control of Benign Prostatic Hyperplasia (BPH). Finasteride causes regression of the enlarged prostate, improves urinary flow and symptoms of BPH. Finasteride reduces the risk of acute urinary retention and the need for surgery including prostatectomy and transurethral resection of the prostate.

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

4. DOSE & DOSE SCHEDULE

See the SPC for full details. The recommended dosages and dose schedules are consistent with those for Proscar 5 mg tablets.

5. TOXICOLOGY

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

6. EFFICACY

No new data on efficacy have been submitted and this is acceptable as the efficacy of Finasteride is well established from many years use in clinical practice.

7. SAFETY

The safety profile for Finasteride is well known and there are no indications that new issues have been identified. The submitted report for the pivotal study includes safety information and confirms that there are apparent new safety issues with the proposed product.

BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data and the pivotal bioequivalence report submitted adequately addressed the previously identified deficiencies. The RMS now accepts that bioequivalence has been adequately demonstrated between the proposed product, Finasteride 5mg Tablets, and the originator (Proscar) and in the absence of any newly identified safety concern considers the overall benefit-risk assessment is favourable. The application is considered to be approvable.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome