

# **Public Assessment Report**

## **Decentralised**

**Finasteride**

**UK/H/983/01/DC**

**Relonchem Limited**

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## Module 1

|   |  |
|---|--|
| <b>Product Name</b>                             | Finasteride 1mg Tablets  |
| <b>Type of Application</b>                      | Standard Abridged Decentralised (Article 10.1)                       |
| <b>Active Substance (INN)</b>                   | Finasteride  |
| <b>Pharmacotherapeutic Classification (ATC)</b> | Testosterone-5-alpha reductase inhibitors (G04CB01)                  |
| <b>Pharmaceutical Form and Strength</b>         | Film-coated Tablet, 1mg  |
| <b>Procedure Numbers</b>                        | <b>UK/H/983/01/DC</b>  |
| <b>RMS</b>                                      | UK   |
| <b>CMS</b>                                      | Ireland  |
| <b>Start Date</b>                               | 22/02/2007   |
| <b>End Date</b>                                 | 11/09/2008   |
| <b>MA Number</b>                                | PL 20395/0068  |
| <b>Name and address of MA holder</b>            | Relonchem Limited<br>27 Old Gloucester Street, London, WC1 3XX<br>UK |

## Module 2

### Summary of Product Characteristics

#### SUMMARY OF PRODUCT CHARACTERISTICS

##### 1 NAME OF THE MEDICINAL PRODUCT

Finasteride 1 mg Tablets

##### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg finasteride.

Also contains 95.55mg Lactose per tablet.

For a full list of excipients, see section 6.1.

##### 3 PHARMACEUTICAL FORM

Film-coated Tablet.

Round biconvex, reddish brown tablets 7mm in diameter, marked "F1"

##### 4 CLINICAL PARTICULARS

###### 4.1 Therapeutic indications

Finasteride is indicated for the treatment of the early stages of androgenetic alopecia in men.

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

###### 4.2 Posology and method of administration

For oral use only

The tablet should be swallowed whole and must not be divided or crushed (see section 6.6).

*Androgenetic alopecia*

The recommended dosage is 1 mg daily. Finasteride may be taken 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 six months and return to baseline by 9 to 12 months.

No data are available on the concomitant use of Finasteride and topical minoxidil in male pattern hair loss.

#### Use in renal insufficiency

No adjustment in dosage is required in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 ml/min), as pharmacokinetic studies did not indicate any change in the disposition of finasteride.

#### Dosage in hepatic insufficiency

There are no data available in patients with hepatic insufficiency (see section 4.4).

#### Use in the elderly

No dosage adjustment is required in elderly patients.

### **4.3 Contraindications**

Finasteride is contraindicated for use in women due to the risk in pregnancy (see 4.6 'Pregnancy and lactation') and in patients with hypersensitivity to finasteride or to any of the excipients.

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

### **4.4 Special warnings and precautions for use**

Clinical trial data is limited to patients with ages from 18 to 49 years, and limited data is available for patients older than 49 years.

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. This decrease in serum PSA concentrations needs to be considered, if during treatment with Finasteride, a patient requires a PSA assay. In this case the PSA value should be doubled before making a comparison with the results from untreated men.

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 foetus (see section 5.3 and 6.6).

Patients with rare hereditary problems of fructose intolerance, galactose intolerance, the Lapp lactase deficiency, galactosaemia or glucose-galactose malabsorption should not take this medicine

#### 4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolising enzyme system. Compounds which have been tested in man have included antipyrine, digoxin, glibenclamide, propranolol, theophylline and warfarin and no interactions were found.

Although specific interaction studies were not performed, in clinical studies finasteride doses of 1 mg or more were used concomitantly with ACE inhibitors, paracetamol, alpha blockers, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H<sub>2</sub> antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

#### 4.6 Pregnancy and lactation

##### *Use during pregnancy*

Finasteride is contra-indicated for use in women due to the risk in pregnancy.

Because of the ability of type II 5 $\alpha$ -reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone (DHT) in some tissues, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

##### *Exposure to finasteride: risk to male foetus*

A small amount of finasteride, less than 0.001% of the 1 mg dose per ejaculation, has been detected in the seminal fluid of men taking finasteride. Studies in Rhesus monkeys have indicated that this amount is unlikely to constitute a risk to the developing male foetus (see Section 5.3).

During continual collection of adverse experiences, post-marketing reports of exposure to finasteride during pregnancy via semen of men taking 1 mg or higher doses have been received for eight live male births, and one retrospectively-reported case concerned an infant with simple hypospadias. Causality cannot be assessed on the basis of this single retrospective report and hypospadias is a relatively common congenital anomaly with an incidence ranging from 0.8 to 8 per 1000 live male births. In addition, a further nine live male births occurred during clinical trials following exposure to finasteride via semen, during pregnancy, and no congenital anomalies have been reported.

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

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 the subsequent potential risk to a male foetus. Finasteride tablets are coated to prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

*Use during lactation*

Finasteride is contraindicated for use in lactation.

#### **4.7 Effects on ability to drive and use machines**

There are no data to suggest that Finasteride affects the ability to drive or use machines.

#### **4.8 Undesirable effects**

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

##### Reproductive system and breast disorders

*Common (>1/100, <1/10):*

Impotence, reduced libido

*Uncommon (>1/1000, < 1/100):*

Ejaculation disorder, reduced volume of ejaculate

*Very rare (< 1/10000), including isolated reports:*

Breast secretion, breast nodules that were surgically removed in single patients

##### Skin and subcutaneous tissue disorders

*Uncommon (>1/1000, < 1/100):*

Skin rash

##### Laboratory tests:

When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels generally decrease in patients treated with finasteride. In a majority of the patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates half of the pre-treatment value. Therefore, in typical patients treated with finasteride for six months or more, PSA values should be doubled for comparison to normal ranges in untreated men. For details and clinical interpretation see section 4.4 (paragraph Effects on prostate-specific antigen (PSA) and prostate cancer detection).

No other difference was observed in patients treated with placebo or finasteride in standard laboratory tests.

### Long-term data

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, of whom 9060 had prostate needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) of men receiving finasteride and in 1147 (24.4%) of men receiving placebo. In the finasteride group, 280 (6.4%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy versus 237 (5.1%) in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of finasteride and tumours with Gleason scores of 7-10 is unknown.

The following undesirable effects have been reported in post-marketing use: ejaculation disorder; breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria and swelling of the lips and face; and testicular pain.

## **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 did not result in side effects.

No specific treatment of overdosage with Finasteride is recommended.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic groups:

Dermatologicals

ATC-Code: D11AX10

Finasteride is a competitive and specific inhibitor of type II 5 $\alpha$ -reductase. 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 $\alpha$ -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 $\alpha$ -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.

#### *Studies in men*

Clinical studies were conducted in 1879 men aged 18 to 41 with mild to moderate, but not complete, vertex hair loss and/or frontal/mid-area hair loss. In the two studies in men with vertex hair loss (n=1553), 290 men completed 5 years of treatment with Propecia vs. 16

patients on placebo. In these two studies, efficacy was assessed by the following methods: (i) hair count in a representative 5.1 cm<sup>2</sup> area of scalp, (ii) patient self assessment questionnaire, (iii) investigator assessment using a seven point scale, and (iv) photographic assessment of standardised paired photographs by a blinded expert panel of dermatologists using a seven point scale.

In these 5- year studies men treated with Finasteride improved compared to both baseline and placebo beginning as early as 3 months, as determined by both the patient and investigator assessments of efficacy. With regard to hair count, the primary endpoint in these studies, increases compared to baseline were demonstrated starting at 6 months (the earliest time point assessed) through to the end of the study. In men treated with Finasteride these increases were greatest at 2 years and gradually declined thereafter to the end of 5 years; whereas hair loss in the placebo group progressively worsened compared to baseline over the entire 5 year period. In Finasteride treated patients, a mean increase from baseline of 88 hairs [ $p < 0.01$ ; 95% CI (77.9, 97.80);  $n=433$ ] in the representative 5.1 cm<sup>2</sup> area was observed at 2 years and an increase from baseline of 38 hairs [ $p < 0.01$ ; 95% CI (20.8, 55.6);  $n=219$ ] was observed at 5 years, compared with a decrease from baseline of 50 hairs [ $p < 0.01$ ; 95% CI (-80.5, -20.6);  $n=47$ ] at 2 years and a decrease from baseline of 239 hairs [ $p < 0.01$ ; 95% CI (-304.4, -173.4);  $n=15$ ] at 5 years in patients who received placebo. Standardised photographic assessment of efficacy demonstrated that 48% of men treated with finasteride for 5 years were rated as improved, and an additional 42% were rated as unchanged. This is in comparison to 25% of men treated with placebo for 5 years who were rated as improved or unchanged. These data demonstrate that treatment with Finasteride for 5 years resulted in a stabilisation of the hair loss that occurred in men treated with placebo.

#### *Studies in women*

Lack of efficacy was demonstrated in post-menopausal women with androgenetic alopecia who were treated with Finasteride in a 12 month, placebo-controlled study ( $n=137$ ). These women did not show any improvement in hair count, patient self-assessment, investigator assessment, or ratings based on standardised photographs, compared with the placebo group.

## **5.2 Pharmacokinetic properties**

### *Absorption*

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 80%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately two hours after dosing and the absorption is complete after six to eight hours.

### *Distribution*

Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 litres.

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<sub>(0-24 hr)</sub> was 53 ng•hr/ml.

Finasteride has been recovered in the cerebrospinal fluid (CSF), but the drug does not appear to concentrate preferentially to the CSF. A small amount of finasteride has also been detected in the seminal fluid of subjects receiving the drug.

### *Biotransformation*

Finasteride is metabolised primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of <sup>14</sup>C-finasteride in man, two metabolites of the drug were identified that possess only a small fraction of the 5 $\alpha$ -reductase inhibitory activity of finasteride.

### *Elimination*

Following an oral dose of <sup>14</sup>C-finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% of total dose was excreted in the faeces.

Plasma clearance is approximately 165 ml/min.

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

### *Characteristics in patients*

No adjustment in dosage is necessary in non-dialysed patients with renal impairment.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and carcinogenic potential.

Reproduction toxicology studies in male rats have demonstrated reduced prostate and seminal vesicular weights, reduced secretion from accessory genital glands and reduced fertility index (caused by the primary pharmacological effect of finasteride). The clinical relevance of these findings is unclear.

As with other 5-alpha-reductase inhibitors, femininisation of male rat foetuses has been seen with administration of finasteride in the gestation period. When finasteride was administered to primates during gestation no femininisation of male foetuses was seen at a blood exposure level well above the expected levels in human semen. It is not likely that exposure of male foetuses to finasteride from semen will cause negative effects.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **Tablet Core**

Lactose monohydrate

Cellulose, microcrystalline

Pregelatinised Starch

Lauroyl Macroglycerides

Sodium starch glycolate – Type A

Magnesium stearate

**Tablet Coating**

Hypromellose 6 cps.

Titanium dioxide (E171)

Iron oxide yellow E 172

Iron oxide red E 172

Macrogol 6000

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions

**6.5 Nature and contents of container**

Blister packs: Aluminium/PVC or Aluminium/Aluminium. Pack size 28 tablets.

Plastic bottles (HDPE) with cap. Pack size 28 tablets.

**6.6 Special precautions for disposal**

Women who are pregnant or may become pregnant should not handle crushed or broken finasteride tablets because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus (see section 4.6)

**7 MARKETING AUTHORISATION HOLDER**

Relonchem Limited, 27 Old Gloucester Street, London, WC1 3XX, UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20395/0068

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11/09/2008

**10 DATE OF REVISION OF THE TEXT**

11/09/2008

## **Module 3**

# **Product Information Leaflet**

**Finasteride 1 mg film-coated tablets**

Finasteride

**RelonChem****PACKAGE LEAFLET: INFORMATION FOR THE USER**

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

**In this leaflet:**

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

**1. What Finasteride tablets are and what they are used for**

Finasteride is used to treat early forms of male pattern hair loss (also called androgenetic alopecia).

**2. Before you take Finasteride tablets**

**Do not take Finasteride tablets if you**

- are allergic (hypersensitive) to finasteride or any of the other ingredients in Finasteride tablets (see section 6)
- are a woman
- are giving to a child.

**Check with your doctor or pharmacist before taking Finasteride tablets if you**

- have difficulty emptying your bladder completely or a greatly reduced flow of urine. Your doctor should examine you before you start taking Finasteride tablets to exclude other obstructions in the urinary tract.

**Taking other medicines**

Finasteride tablets can normally be taken with other medicines. Please ask your doctor or pharmacist before you take other medicines at the same time or if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**2. Special precautions**

Finasteride tablets are only intended for men.

**Pregnancy**

**Women who are pregnant or may become pregnant should not handle broken or crushed Finasteride tablets.** If finasteride is absorbed through the skin or taken by mouth by a woman pregnant with a male foetus, the child may be born with malformed genital organs. The tablets are film-coated, which prevents contact with finasteride provided the tablets are not broken or crushed.

If your sexual partner is or may possibly be pregnant, you must avoid exposing her to your semen, which could contain a small amount of the drug by using a condom. If you think a pregnant woman has come into contact with finasteride, you should consult a doctor.

**Driving and using machines**

There is no evidence to suggest that Finasteride tablets affect the ability to drive or use machines.

**Important information about some of the ingredients of Finasteride Tablets**

Finasteride tablets contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine

**Blood tests**

Finasteride tablets can affect a blood test called PSA. If you have a PSA test done, tell your doctor you are taking Finasteride tablets.

**3. How to take Finasteride tablets**

Always take Finasteride tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

**Usual doses are**

1mg (1 tablet) daily.

The tablet should be **swallowed whole** and **should not be broken or crushed**. It may be taken **with or without food**.

**If you stop taking Finasteride tablets**

Although an improvement is often noticed after a short time, it may be necessary to continue the treatment for at least 6 months.

**Do not alter the dose or stop treatment without asking your doctor.**

**If you take more Finasteride tablets than you should**

If you (or someone else) swallow a lot of the tablets at the same time, or you think a child has swallowed any of the tablets, contact your nearest hospital casualty department or your doctor immediately.

**If you forget to take Finasteride tablets**

Do not take a double dose to make up for a forgotten tablet. Just take the next one when it is due.

**If you forget to take Finasteride tablets**

Do not take a double dose to make up for a forgotten tablet. Just take the next one when it is due.

**4. Possible side effects**

Like all medicines, Finasteride tablets can cause side effects, although not everybody gets them.

**Stop taking Finasteride tablets and contact your doctor immediately if you develop any of the following symptoms of an allergic reaction:** swelling of the face, tongue or lips or urticaria (itchy skin rash).

**Please tell your doctor or pharmacist** if you notice any of the following effects or any side effects not listed.

**Common** (occur in more than 1 in 100 users but less than 1 in 10 users): inability to obtain an erection, reduced sex drive.

**Uncommon** (occur in less than 1 in 100 users): Difficulty ejaculating, rash, reduced amount of ejaculatory fluid.

**Very rare** (occur in less than 1 in 10,000 users): leaking fluid from the male breasts, occasionally a lump which may need to be surgically removed from the male breast.

The following undesirable effects have been reported in post-marketing use: breast tenderness and enlargement; and testicular pain.

**5. How to store Finasteride tablets**

Keep out of the reach and sight of children. Do not use Finasteride Tablets after the expiry date which is stated on the blister, carton or bottle after 'Expiry date:'. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. Further information****What Finasteride tablets contain**

- the active substance is finasteride 1 mg
- the other ingredients are lactose monohydrate, microcrystalline cellulose, pregelatinised starch, lauroyl macroglycerides, sodium starch glycolate Type A, magnesium stearate, hypromellose, titanium dioxide (E171), yellow and red iron oxide (E172), and macrogol 6000.

**What Finasteride tablets look like and contents of the pack**

Finasteride 1 mg film-coated tablets are round, biconvex reddish-brown tablets, with the markings 'F1'

They are supplied in:

Blister packs containing 28 tablets

Plastic bottles containing 28 tablets

**Marketing Authorisation Holder**

Relonchem Limited,  
27, Old Gloucester street, London, WC1 3XX.

**Manufacturer**

Actavis hf, Reykjavikurvegur 78, IS-220 Hafnarfjordur, Iceland.

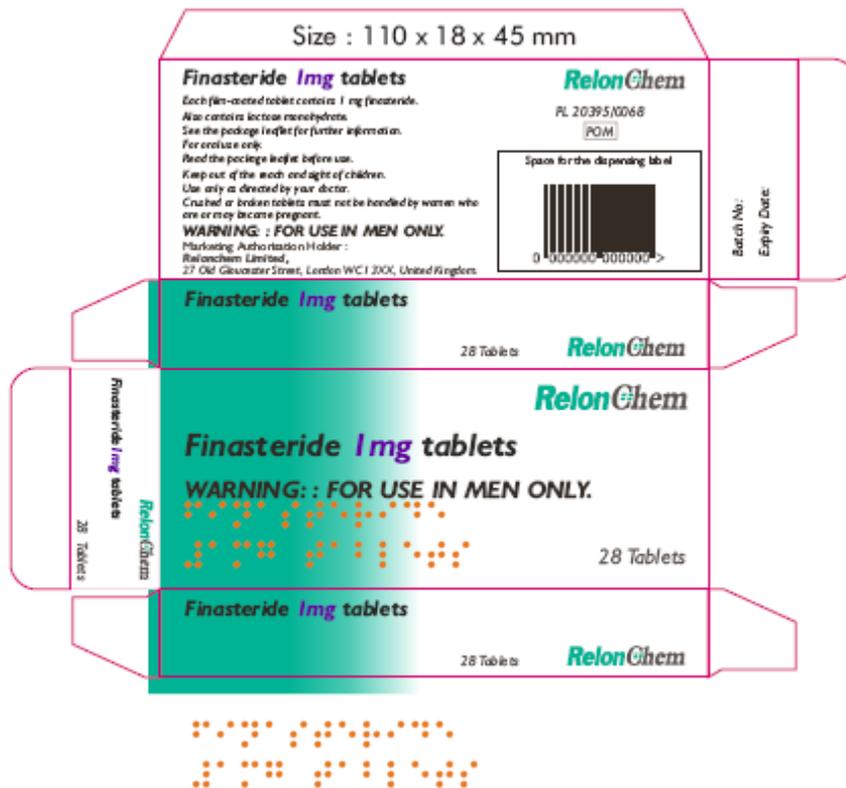
MA Number: PL 20395/0068

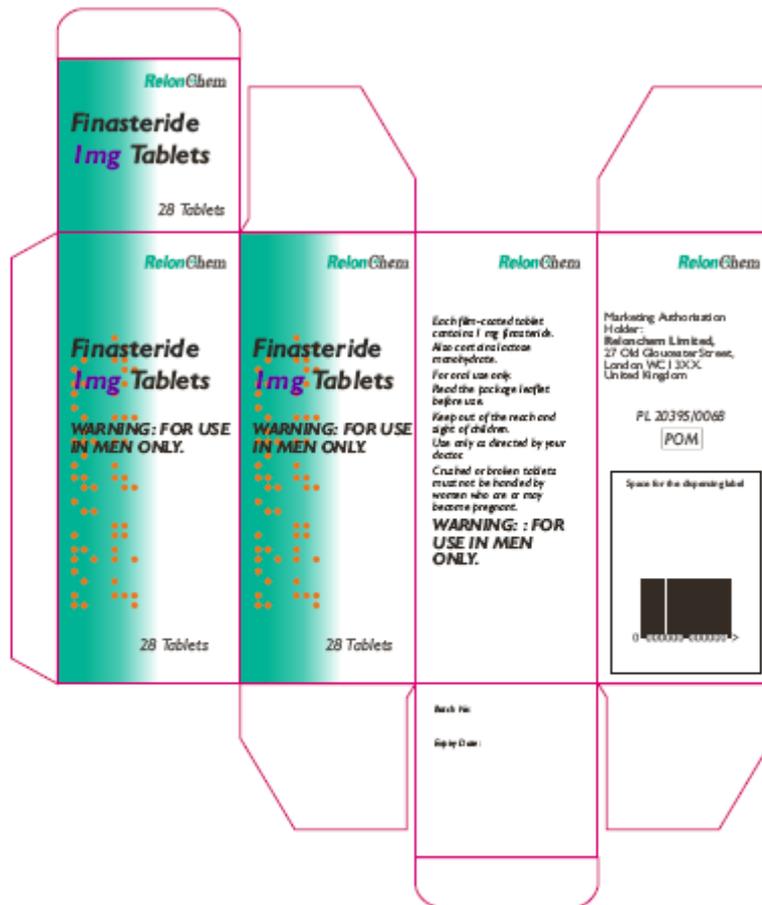
**This leaflet was last approved in (mm/yyyy)**

Revision Date: August 2008

# Module 4

## Labelling





The Batch and Expiry Date will be embossed on to the actual cartons.

\*XX - 50, 75 or 100 tablets. Only the marketed pack sizes will be stated on the actual printed carton.



## Module 5

### Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Finasteride 1mg Tablets, in the treatment of men with male pattern hair loss was approvable. Satisfactory responses were given to the preliminary list of questions raised during the assessment.

The applicant submitted the application of Finasteride 1 mg tablets in the treatment of male pattern hair loss via the decentralised procedure with IE as the only CMS.

The applicant also applied for the therapeutic indications for the treatment of benign prostatic hyperplasia and male pattern hair loss. Major public health concerns were raised by IE during the 100 days of the procedure, since the indication for the treatment of benign prostatic hyperplasia was not acceptable for CMS. The applicant withdrew the application from Ireland.

Finasteride is marketed in two strengths. 5 mg tablets (Proscar) have been authorised for the treatment of benign prostatic hyperplasia. 1 mg tablets (Propecia) have been licensed for the treatment of male pattern hair loss. Administration of 5 tablets (5 x 1 mg) as a single dose is not considered as a good clinical practice and may impair patient compliance.

The applicant has answered adequately to all issues raised. The therapeutic indication benign prostatic hyperplasia has been deleted. The proposed therapeutic indication is the early stages of androgenetic alopecia in men. The product labelling has been updated according to the issues raised during the procedure. This procedure run in parallel with the UK/H/1076-1081/01/DC (PL 24668/0026-31) and the final product labelling was harmonised for these parallel procedures.

#### EXECUTIVE SUMMARY

##### Problem statement

This is a decentralised application for a marketing authorization for a medicinal product – so called “generic application”, finasteride 1 mg tablets of Relonchem Ltd, UK submitted under Article 10.1. The company claims essential similarity to the reference products Propecia 1 mg tablets (PL 00025/0351 – 0028) and Proscar 5 mg tablets (PL 00025/0279) (MSD, UK). Ireland is a CMS.

This decentralised application is going in parallel with  
UK/H/1076-1078/01/DC- DE  
UK/H/1079-1080/01/DC- IT  
UK/H/1081/01/DC- DE, ES, IT

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence A bioequivalence study should be submitted for the immediate release product to claim essential similarity with the reference product. The Applicant has submitted a single dose BE study under fasting conditions to support the application.

##### About the product

The active compound in Finasterid tablets is finasteride, a competitive and specific inhibitor of the enzyme steroid type II 5 $\alpha$ -reductase, which catalyses the 5 $\alpha$ -reduction of testosterone to the more potent androgen dihydrotestosterone (DHT). Finasteride is chemically similar to testosterone but does not affect the binding of testosterone or DHT to the androgen receptor, nor does it possess any steroid hormone-related properties.

Therefore, the major effect of finasteride is to decrease prostatic and circulating DHT levels.

Finasteride is indicated for the treatment of male pattern hair loss (1 mg daily) and for the treatment

and control of symptoms of benign prostate hyperplasia (5 mg daily).

### **General comments on the submitted dossier**

The Finasteride product submitted with this application is considered generic of the reference medicinal product Propecia as it satisfies the criteria of having the same qualitative and quantitative composition in terms of active ingredients, the same pharmaceutical form and is considered bioequivalent with the reference 1mg medicinal product.

The submitted dossier is adequate and sufficient.

### **General comments on compliance with GMP, GLP, GCP and agreed ethical principles.**

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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 of 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.

## **SCIENTIFIC OVERVIEW AND DISCUSSION**

### **Quality aspects**

#### **Drug substance**

The chemical-pharmaceutical documentation and Expert Report in relation to Finasteride 1mg tablets are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up with minor amendments required.

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period is not confirmed by the finished product manufacturers, however, data to support a two year re-test period is provided in the Drug Master File.

#### **Drug Product**

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on five batches. The batch analysis results show that the finished products meet the specifications proposed..

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

The proposed shelf-life of 36 months with no storage conditions to be specified for the drug product is considered acceptable if the limit for Ph Eur impurity A is confirmed to be acceptable and if the microbiological quality of the product is demonstrate at the proposed shelf-life.

## Non clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of finasteride are well known. As finasteride is a well known active substance, no further studies are required and the applicant has not provided any.

## Clinical aspects

### Pharmacokinetics

The oral bioavailability of finasteride is approximately 80%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately two hours after dosing. Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 litres. Finasteride is metabolised primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of <sup>14</sup>C-finasteride in man, two metabolites of the drug were identified that possess only a small fraction of the 5 $\alpha$ -reductase inhibitory activity of finasteride. Following an oral dose of <sup>14</sup>C-finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% of total dose was excreted in the faeces. Plasma clearance is approximately 165 ml/min. The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age.

Applicant has conducted a single dose BE study to support the application and confirm that the product under investigation is essentially similar to the reference product.

### Bioequivalence study

A single dose, randomised, two-period, crossover bioequivalence study was conducted in 36 healthy male volunteers with age range from 18 to 48 years. Study drug, test or reference 1 mg finasteride film-coated tablet, was administered after an overnight fast with 240 ml water. 19 blood samples were collected at 0 predose and at prespecified timepoints up to 36 hours postdose with washout period of 7 days between study periods.

### Test and reference products

Finasteride 1 mg film-coated tablets (test) manufactured by Omega Farma ehf, Iceland (batch No. 731853, exp. date Sept 2004) has been compared to Propecia® 1 mg film-coated tablets (reference) manufactured by MSD, UK (batch No: 226518, exp. date Sept 2005).

### Pharmacokinetic Variables

Pharmacokinetic parameters C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, T<sub>max</sub>, T<sub>1/2</sub> were determined.

### Statistical methods

Statistical analysis was performed using BIOPRO (ver 3.2). ANOVA model included sequence, subject nested into sequence, period and formulation effects. 90% CI of the ratio of C<sub>max</sub> and AUC after ln-transformation of the data was calculated.

## Results

**Table 1: Summary of pharmacokinetic data for finasteride**  
(n = 36; Dose: 1 x 1 mg finasteride film-coated tablet)

| Propecia® (Reference product)        |                     |             |
|--------------------------------------|---------------------|-------------|
| Variable                             | Geometric mean (SD) | Range       |
| AUC(0-∞) (ng·h/ml)                   | 45.2 (14.2)         | 20.8 – 81.6 |
| AUC (0-t <sub>last</sub> ) (ng·h/ml) | 43.7 (13.8)         | 19.8 – 78.2 |
| C <sub>max</sub> (ng/ml)             | 8.16 (1.91)         | 3.79 – 10.9 |

**Table 1: Summary of pharmacokinetic data for finasteride**  
(n = 36; Dose: 1 x 1 mg finasteride film-coated tablet)

| Finasteride (Test product)           |                     |             |
|--------------------------------------|---------------------|-------------|
| Variable                             | Geometric mean (SD) | Range       |
| AUC(0-∞) (ng·h/ml)                   | 47.1 (13.8)         | 22.1 – 71.5 |
| AUC (0-t <sub>last</sub> ) (ng·h/ml) | 45.7 (13.4)         | 21.0 – 69.7 |
| C <sub>max</sub> (ng/ml)             | 8.05 (1.98)         | 3.78 – 11.7 |

**Table 2: Test vs Reference**

| Variable                             | Point estimate (%) | 90% Confidence interval |
|--------------------------------------|--------------------|-------------------------|
| AUC(0-∞) (ng·h/ml)                   | 104                | 99.3 ; 110              |
| AUC (0-t <sub>last</sub> ) (ng·h/ml) | 105                | 99.4 ; 110              |
| C <sub>max</sub> (ng/ml)             | 98.6               | 93.5 ; 104              |

Both formulations were well tolerated with no unexpected adverse events or serious adverse events.

**Assessor's comment:**

Bioequivalence study submitted by the applicant was performed according to the CPMP/EWP/QWP/1401/98 NfG and GCP requirements.

The 90% confidence intervals for AUC and C<sub>max</sub> lie within the acceptance criteria of 80-125%.

Therefore, bioequivalence was demonstrated after a single dose (1 mg) administration of two formulations of finasteride under fasting conditions.

## Pharmacodynamics

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.

## Clinical efficacy

No new efficacy data have been submitted and none are required for this application.

**Clinical safety**

No new safety data have been submitted and none are required for this application.

**Readability testing of the Patient Information Leaflet.**

Readability testing was carried out on the PIL and assessed by MHRA as part of the application and was found to be satisfactory.

**BENEFIT RISK ASSESSMENT**

The benefit-risk ratio is considered favourable.

## **Module 6**

### **Steps taken after procedure**

No non-confidential alterations have been made to the market authorisation.