IPAR

IRISH MEDICINES BOARD

Scientific discussion

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Finasteride 5mg Film Coated Tablets

FINASTERIDE

PA1286/044/001

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Finasteride 5mg Film-coated Tablets from Merck Sharp & Dohme Ireland Human Health Ltd. on 28th February 2014 for the treatment and control of benign prostatic hyperplasia (BPH) and for the prevention of urologic events to reduce the risk of acute urinary retention and to reduce the risk of surgery including transurethral resection of the prostate (TURP) and prostatectomy.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Proscar 5mg Film-coated Tablets, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Finasteride 5mg Film-coated Tablets. Finasteride 5mg Film-coated Tablets have the same qualitative and quantitative composition in terms of the active substance and the same pharmaceutical form as Proscar 5mg Film-coated Tablets.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product	Finasteride
Name(s) of the active substance(s) (INN)	FINASTERIDE
Pharmacotherapeutic classification (ATC code)	G04CB01
Pharmaceutical form and strength(s)	5mg Film Coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1286/044/001
Marketing Authorisation Holder	Merck Sharp & Dohme Ireland

II QUALITY ASPECTS

II.1. Introduction

This application is for Finasteride 5mg Film-coated Tablets.

II.2 Drug substance

The active substance is Finasteride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The medicinal product comprises of film-coated tablets, each containing 5mg finasteride combined with microcrystalline cellulose, docusate sodium, magnesium stearate, lactose monohydrate, pregelatinised maize starch, sodium starch glycolate (Type A), yellow iron oxide (E172), hydroxypropylcellulose, indigo carmine aluminium lake (E132), hypromellose, talc and titanium dioxide (E171).

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as blisters consisting of opaque PVC/PE/PVdC lidded with aluminium foil.

Evidence has been provided that the blisters comply with Ph. Eur. and EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years when stored below 30°C in the original package.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Finasteride 5mg Film-coated Tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Proscar 5mgs PA 1286/17/1 which is marketed in Ireland. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

See clinical section.

III.3 Pharmacokinetics

See clinical section.

III.4 Toxicology

As this an informed consent application, additional toxicology tests not required.

III.5 Ecotoxicity/environmental risk assessment

Not Applicable as this is an informed consent application.

III.6 Summary of the non-clinical aspects

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.
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 (1 to 1000 times the recommended human dose of 5 mg/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, and transient nipple development when given finasteride at doses $\geq$ 30 µg/kg/day ($\geq$30% of the recommended human dose of 5 mg/day), and decreased anogenital distance when given finasteride in doses $\geq$ 3 µg/kg/day ($\geq$ 3% of the recommended human dose of 5 mg/day). The critical period during which these effects can be induced has been defined in rats as days 16-17 of gestation.

Intravenous administration of finasteride to pregnant rhesus monkeys at doses up to 800 ng/day during the entire period of embryonic and foetal development resulted in no abnormalities in male foetuses. This dose is about 60-120 times higher than the estimated amount in semen of a man who have taken 5 mg finasteride, and to which a woman could be exposed via semen. In confirmation of the relevance of the Rhesus model for human foetal development, oral administration of finasteride 2 mg/kg/day (the systemic exposure (AUC) of monkeys was slightly higher (3x) than that of men who have taken 5 mg finasteride, or approximately 1-2 million times the estimated mount of finasteride in semen) to pregnant monkeys resulted in external genital abnormalities in male foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses at any dose.

IV CLINICAL ASPECTS

IV.1 Introduction

Finasteride is a well known active substance with established efficacy and tolerability. This medicinal product is the same as Proscar 5mgs PA 1286/17/1 on the European market. As such, no clinical data have been submitted or assessment has been made on the application. This is acceptable for this type of application.
The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Proscar 5mgs PA 1286/17/1 marketed by MSD Ireland Human Health Ltd

IV.2 Pharmacokinetics

After an oral dose of ^{14}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. Two metabolites have been identified which possess only a small fraction of the 5 α-reductase activity of finasteride.

The oral bioavailability of finasteride is approximately 80%, relative to an intravenous reference dose, and is unaffected by food. Maximum plasma concentrations are reached approximately two hours after dosing and the absorption is complete within 6−8 hours. Protein binding is approximately 93%. Plasma clearance and the volume of distribution are approximately 165 ml/min and 76 l, respectively.

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

In patients with chronic renal impairment, whose creatinine clearance ranged from 9 to 55 ml/min, the disposition of a single dose of ^{14}C-finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites which normally is excreted renally was excreted in the faeces. It therefore appears that faecal excretion increases commensurate to the decrease in urinary excretion of metabolites. Dosage adjustment in non−dialysed patients with renal impairment is not necessary.

There are no data available in patients with hepatic insufficiency.

Finasteride has been found to cross the blood−brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated patients.

IV.3 Pharmacodynamics

Finasteride is a competitive inhibitor of human Type II 5 α-reductase, an intracellular enzyme which metabolises testosterone into the more potent androgen, dihydrotestosterone (DHT). In benign prostatic hyperplasia (BPH), enlargement of the prostate gland is dependent upon the conversion of testosterone to DHT within the prostate. 'Finasteride' is highly effective in reducing circulating and intraprostatic DHT. Finasteride has no affinity for the androgen receptor.

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.

Medical therapy of prostatic symptoms

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a 4- to 6-year study in 3047 men with symptomatic BPH who were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/day and doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency, recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with finasteride, doxazosin, or combination therapy resulted in a significant reduction in the risk of clinical progression of BPH by 34(p=0.002), 39 (p<0.001), and 67% (p<0.001), respectively. The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%), and 64% (95% CI 48 to 75%) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67 (p=0.011), 31 (p=0.296), and 79% (p=0.001) in the finasteride, doxazosin, and combination groups, respectively, compared to placebo. Only the finasteride and combination therapy groups were significantly different from placebo.

* Titrated from 1 mg to 4 or 8 mg as tolerated over a 3-week period.

IV.4 / IV.5 Clinical Efficacy and Safety

As this is an informed consent efficacy and safety is expected to be similar to the reference Proscar 5mgs PA 1286/17/1 marketed by MSD Ireland Human Health Ltd.

The RMP is acceptable. A summary of the ongoing safety concerns are as follows:

Important identified risks	Exposure during pregnancy Off-label use in women and adolescents
Important potential risks	Persistence of erectile dysfunction Male infertility Depressive disorders Male breast cancer

Routine pharmacovigilance is recommended and this is acceptable.

PSURs should be submitted according to legal requirements.

The marketing authorisation holder (MAH) submitted a summary describing the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

Finasteride is a well known substance and as this is an informed consent efficacy and safety is expected to be similar to the reference Proscar 5mgs PA 1286/17/1 marketed by MSD Ireland Human Health Ltd.
The product information SmPC and patient leaflet are the same as the reference. No new efficacy or safety data have been submitted and are not required for this application, as it is an informed consent application.
Overall benefit/risk is favourable.

V OVERALL CONCLUSIONS

The overall assessment outcome of Finasteride 5mg Film-coated Tablets is positive.

Finasteride 5mg Film-coated Tablets is the same as Proscar 5mg Film-coated Tablets. Proscar is a well-known medicinal product with a proven chemical-pharmaceutical quality and clinical efficacy and safety is established and favourable.

The IMB, on the basis of the data submitted considered that Finasteride 5mg Film-coated Tablets was the same as the reference product and therefore granted a marketing authorisation.