Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Finasteride Ranbaxy 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 5 mg finasteride.

Excipient: One film-coated tablet contains 75 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex, film-coated tablet, diameter 7 mm, embossed “F” and “5” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Finasteride Ranbaxy is indicated for the treatment and control of benign prostatic hyperplasia (BPH) to:

- cause regression of the enlarged prostate, improve urinary flow and improve the symptoms associated with BPH
- reduce the incidence of acute urinary retention and the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

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

4.2 Posology and method of administration

For oral use only.

The recommended dosage is one 5 mg tablet daily with or without food. The tablet should be swallowed whole and must not be divided or crushed (see section 6.6). Even though improvement can be seen within a short time, treatment for at least 6 months may be necessary in order to determine objectively whether a satisfactory response to treatment has been achieved.

Dosage in hepatic insufficiency

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

Dosage in renal insufficiency

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

Dosage in the elderly

Dosage adjustments are not necessary although pharmacokinetic studies have shown that the elimination rate of finasteride is slightly decreased in patients above 70 years of age.

4.3 Contraindications

Hypersensitivity to finasteride or to any of the excipients.

Contra-indicated in women who are or may potentially become pregnant (see sections 4.4, 4.6 and 6.6).

Finasteride is not indicated either in women or in children.

4.4 Special warnings and precautions for use

General:

Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.Consultation of an 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.

Breast cancer has been reported in men taking finasteride during clinical trials and in the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

There is no experience in patients with hepatic insufficiency. Since finasteride is metabolized in the liver (see section 4.2) caution is advised in patients with impaired hepatic function as the plasma levels of finasteride may be increased in such patients

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

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

Serum PSA concentration is correlated with patient age and prostatic volume, and prostatic volume is correlated with patient age. Digital rectal examination, and, if necessary, determination of prostate-specific-antigen (PSA) in serum should be carried out on patients prior to initiating therapy with finasteride and periodically during treatment to rule out prostate cancer. There is considerable overlap in PSA levels among men with and without prostate cancer. Therefore, in men with BPH, PSA values within the normal reference range do not rule out prostate cancer regardless of treatment with finasteride.

Finasteride causes a decrease in serum 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 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 values, although it may vary in individual patients. In patients treated with finasteride for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity or 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 to finasteride therapy. Percent 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.

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

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 fetus. Finasteride tablets have a film coating which prevents contact with the active ingredient provided that the tablets have not been broken or crushed (see sections 4.6 and 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant drug interactions have been identified. Finasteride does not appear to affect the cytochrome P450 enzyme system. The following medicinal products have been investigated in man and no clinically significant interactions have been found: propranolol, digoxin, glibenclamide, warfarin, theophylline and antipyrine. No meaningful interactions were found.

Other concomitant therapy:
Although specific interaction studies were not performed in clinical studies, finasteride was used concomitantly with ACE inhibitors, alpha-blockers, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H2 antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin and paracetamol, quinolones and benzodiazepines without evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy: Finasteride is contra indicated during pregnancy.

Finasteride is not indicated in women.

Because of the ability of 5α-Reductase-inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, might cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman (See section 5.3).

Exposure to finasteride - risk to male fetus.

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 fetus (see section 6.6).

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

Lactation

Finasteride 5 mg tablets are not indicated for use in women. It is not known whether finasteride is excreted in breast milk.

4.7 Effects on ability to drive and use machines

There is no available data indicating that finasteride would have an influence on the ability to drive or to use machines.

4.8 Undesirable effects

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

The adverse reactions during clinical trials and/or post-marketing use are listed below.

Frequency of adverse reactions is determined as follows:
Very Common (

≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥1/10,000, < 1/1,000);
Very rare (< 1/10,000); not known (cannot be estimated from the available data).

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.

Immune system disorders
Not known: Hypersensitivity reactions including pruritus, urticaria and swelling of the face and lips

Skin and subcutaneous tissue disorders
Common: Skin rash
Rare: Pruritus, Urticaria

Nervous system disorders
Rare Somnolence

Psychiatric disorders:
Uncommon: Decreased libido (incidences presented as difference from placebo in clinical studies at month 12)

Nervous system disorders:
Rare: Somnolence

Cardiac disorders:
Not known: Palpitation

Hepatobiliary disorders

Not known: Increased hepatic enzymes
Reproductive system and breast disorders:
Very common: Impotence
Uncommon*: Erectile dysfunction, ejaculation disorder (including decreased volume of ejaculate).
Very Rare: Breast secretion, breast nodules
Not known: Breast tenderness and enlargement, Testicular pain, infertility**.
**See section 4.4.

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

In addition, the following have been reported in postmarketing use: persistence of erectile dysfunction after discontinuation of treatment with finasteride; male breast cancer (see section 4.4 Special warnings and precautions for use).

Medical therapy of prostatic symptoms (MTOPS)

The MTOPS study compared finasteride 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder events without regard to drug relationship were: finasteride 8.3%, doxazosin 5.3%, combination 15.0%, placebo 3.9%. Besides adverse reactions related to “Nervous system disorders” were also observed with a greater frequency in patients receiving the combination (see table below).

System organ class	Placebo N = 737 N= 737	Doxazosin N = 756 N=756	Finasteride N = 768 N=768	Finasteride + Doxazosin N =786 N=786
	%	%	%	%
Patients with one or more undesirable effect	46.4	64.9	52.5	73.8
General disorders	11.7	21.4	11.6	21.5
Asthenia	7.1	15.7	5.3	16.8
Cardiac disorders	10.4	23.1	12.6	22.0
Hypotension Orthostatic hypotension	0.7 8.0	3.4 16.7	1.2 9.1	1.5 17.8
Nervous system disorders	16.1	28.4	19.7	36.3
Dizziness Reduced libido Somnolence	8.1 5.7 1.5	17.7 7.0 3.7	7.4 10.0 1.7	23.2 11.6 3.1
Uro-genital disorders	18.6	22.1	29.7	36.8
Ejaculation disorders Breast enlargement Impotency Other sexual abnormalities	2.3 0.7 12.2 0.9	4.5 1.1 14.4 2.0	7.2 2.2 18.5 2.5	14.1 1.5 22.6 3.1

Laboratory tests:

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 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.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Testosterone-5α-reductase-inhibitors

ATC-Code: G 04 CB 01

Finasteride is a synthetic 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme Type-II-5α-reductase. The enzyme converts testosterone into the more potent androgen dihydrotestosterone (DHT). The prostate gland and, consequently, also the hyperplasic prostate tissue are dependent on the conversion of testosterone to DHT for their normal function and growth. Finasteride has no affinity for the androgen receptor.

Clinical studies show a rapid reduction of the serum DHT levels of 70%, which leads to a reduction of prostate volume. After 3 months, a reduction of approx. 20% in the volume of the gland occurs, and the shrinking continues and reaches approx. 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 urine 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

The bioavailability of finasteride is approx. 80%. Peak plasma concentrations are reached approx. 2 hours after intake, and absorption is complete after 6-8 hours.

Distribution

Binding to plasma proteins is approx. 93%.

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.

Biotransformation:

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

Elimination:

The plasma half life averages 6 hours (4-12 hours) (in men > 70 years: 8 hours, range 6 – 15 hours). After administration of radioactively labelled finasteride, approx. 39% (32 – 46%) of the dose is excreted in the urine in the form of metabolites. Virtually no unchanged finasteride is recovered in the urine. Approx. 57% (51 – 64%) of the total dose is excreted in the faeces.

In patients with impaired renal function (creatinine clearance as low as 9 ml/min), no changes in the elimination of finasteride have been seen (see section 4.2).

Finasteride has been found to cross the blood-brain barrier. Small amounts of finasteride have been recovered in the seminal fluid of treated. In 2 studies of healthy subjects (n=69) receiving finasteride 5 mg/day for 6-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/ml) to 10.54 ng/ml. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving finasteride 5 mg/day ranged from undetectable (<1.0 ng/ml) to 21 ng/ml. Thus, based on a 5-ml ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 μg) that had no effect on circulating DHT levels in men (see also section 5.3.)

In patients with chronic renal impairment, whose creatinine clearance ranged from 9-55 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.

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. Intravenous administration of finasteride to pregnant rhesus monkeys at doses as high as >800 ng/day during the entire period of embryonic and foetal 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

Pregelatinised starch (maize)

Sodium starch glycolate, type A

Magnesium stearate

Sodium laurilsulfate

Film-coating:

Hypromellose

Cellulose microcrystalline

Macrogol stearate (type I)

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 PVC/PVDC/Aluminium: 15,28,30,50,98,100

Bottles (HDPE containers with PP child proof screw caps): 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Ranbaxy (UK) Ltd
20 Balderton Street
London W1K
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 967/15/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14th December 2007

10 DATE OF REVISION OF THE TEXT

October 2010