

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Finasteride Teva 5 mg 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 Teva 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 Teva 5 mg tablets should 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

Finasteride is contraindicated in the following:

- Hypersensitivity to finasteride or to any of the excipients.
- Pregnancy – Use in women who are or may potentially be pregnant (see sections 4.6 and 6.6).

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

4.4 Special warnings and precautions for use

General

To avoid obstructive complications it is important that patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored. The possibility of surgery should be an option.

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.

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.

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

No clinical benefit has yet been demonstrated in patients with prostate cancer treated with finasteride. Patients with BPH and elevated serum prostate specific antigen (PSA) were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these BPH studies, finasteride did not appear to alter the rate of prostate cancer detection, and the overall incidence of prostate cancer was not significantly different in patients treated with finasteride or placebo.

Digital rectal examinations as well as other evaluations for prostate cancer are recommended prior to initiating therapy with finasteride and periodically thereafter. Serum PSA is also used for prostate cancer detection. Generally a baseline PSA > 10 ng/ml (Hybritech) prompts further evaluation and consideration of biopsy; for PSA levels between 4 and 10 ng/ml, further evaluation is advisable. 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. A baseline PSA < 4 ng/ml does not exclude prostate cancer.

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. Analysis of PSA data from over 3000 patients in the 4-year, double-blind, placebo-controlled finasteride Long-Term Efficacy and Safety Study (PLESS) confirmed that in typical 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 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 to therapy with finasteride.

Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride. The ratio of free to total PSA 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 to its value is necessary.

*Drug/laboratory test interactions**Effect on levels of PSA*

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 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 stabilize to a new baseline. The post-treatment baseline approximates half of the pretreatment 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 clinical interpretation, see section 4.4 "Special warnings and precautions for use", Effects on PSA and prostate cancer detection.

Breast cancer in men

Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and the postmarketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.

Paediatric population

Finasteride is not indicated for use in children. Safety and effectiveness in children have not been established.

Lactose

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.

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 significantly the cytochrome P450-linked drug metabolizing enzyme system. Compounds which have been tested in man have included propranolol, digoxin, glyburide, warfarin, theophylline and antipyrine and no clinically 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**

Finasteride is contraindicated for use in women when they are or may potentially be pregnant (see section 4.3).

Because of the ability of finasteride to inhibit conversion of testosterone to dihydrotestosterone (DHT) finasteride may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman.

Exposure to finasteride – risk to male fetus

Women should not handle crushed or broken finasteride tablets when they are or may potentially be pregnant 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 during normal handling, provided that the tablets have not been broken or crushed.

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. When the patient's sexual partner is or may potentially be pregnant, the patient is recommended to minimise exposure of his partner to semen.

Breast-feeding

Finasteride is not indicated for use in women.
It is not known whether finasteride is excreted in human 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 reactions are impotence and reduced libido. These reactions 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 reported during clinical trials and/or post-marketing use are listed below.

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000; including isolated reports), not known (cannot be estimated from the available data).

<i>Immune system disorders</i>	
Not known:	Hypersensitivity reactions including swelling of lips and face
<i>Psychiatric disorders</i>	
Common:	Decreased libido
<i>Nervous system disorders</i>	
Uncommon:	Somnolence
<i>Cardiac disorders</i>	
Not known:	Palpitation
<i>Hepatobiliary disorders</i>	
Not known:	Increased hepatic enzymes
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon:	Rash
Not known:	Pruritus, urticaria
<i>Reproductive system and breast disorders</i>	
Common:	Impotence
Uncommon:	Ejaculation disorder, breast tenderness, breast enlargement
Not known:	Testicular pain
<i>Investigations</i>	
Common:	Decreased volume of ejaculate

In addition, the following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4).

Medical therapy of prostate 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 in patients receiving combination therapy was comparable to the sum of incidences of this adverse experience for the two monotherapies.

System organ class	Placebo N = 737	Doxazosin N = 756	Finasteride N = 768	Finasteride + Doxazosin 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	0.7	3.4	1.2	1.5
Orthostatic 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
Reduced libido	5.7	7.0	10.0	11.6
Somnolence	1.5	3.7	1.7	3.1
Uro-genital disorders	18.6	22.1	29.7	36.8
Ejaculation disorders	2.3	4.5	7.2	14.1
Breast enlargement	0.7	1.1	2.2	1.5
Impotency	12.2	14.4	18.5	22.6
Other sexual abnormalities	0.9	2.0	2.5	3.1

Other 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%) men receiving finasteride and 1147 (24.4%) men receiving placebo. In the finasteride group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Additional analyses suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride group may be explained by a detection bias due to the effect of finasteride on prostate volume. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2) at diagnosis. The clinical significance of the Gleason 7-10 data is unknown.

Laboratory test findings

When PSA laboratory determinations are evaluated, consideration should be given to the fact that PSA levels are decreased in patients treated with finasteride (see section 4.4).

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-5 α -reductase-inhibitors

ATC-Code: G 04 CB 01

Finasteride is a synthetic 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme Type-II-5 α -reductase. The enzyme converts testosterone into the more potent androgen 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. 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 QUASJH-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 P450 enzyme system. Two metabolites with low 5 α -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 patients. 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 ¹⁴C-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, 50 x 1, 98, 100, 100 x 1

Bottles (HDPE): 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

Teva Pharma B.V
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/35/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th February 2008

Date of last renewal: 1st May 2011

10 DATE OF REVISION OF THE TEXT

May 2012