SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Finasteride 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 5 mg finasteride.

Excipient with known effect: One film-coated tablet contains 108 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Blue, capsule-shaped film-coated tablet, debossed “FNT5” on one side and plain on the other

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The recommended dosage is one 5 mg tablet daily 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.

Hepatic impairment

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

Renal impairment

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.

Older people

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.

Method of administration

For oral use only.

The tablet can be taken with or without food. The tablet should be swallowed whole and must not be divided or crushed (see section 6.6).

4.3 Contraindications

Finasteride is contraindicated in the following:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pregnancy – Use in women when they are or may potentially be pregnant (see sections 4.6 and 6.6).

Finasteride is not indicated for use in women or children.

4.4 Special warnings and precautions for use

General

To avoid obstructive complications it is important that patients with large residual urine and/or heavily decreased urinary flow are carefully controlled. 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 5 mg. 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 5 mg 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 5 mg or placebo.

Digital rectal examinations as well as other evaluations for prostate cancer are recommended prior to initiating therapy with finasteride 5mg 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 5 mg. A baseline PSA < 4 ng/ml does not exclude prostate cancer.

Finasteride 5 mg 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 5 mg 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 5 mg 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 5 mg should be carefully evaluated, including consideration of non-compliance to therapy with finasteride 5 mg.

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 5 mg. 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 pre-treatment value. Therefore, in typical patients treated with finasteride 5 mg 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.

Percent free PSA (free to total PSA ratio) is not significantly decreased by finasteride 5 mg. The ratio of free to total PSA remains constant even under the influence of finasteride 5 mg. When percent free PSA is used as an aid in the detection of prostate cancer, no adjustment to its value is necessary.

Breast cancer in men

Breast cancer has been reported in men taking finasteride 5 mg during clinical trials and 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.

Mood alterations and depression

Mood alterations including depressed mood, depression and, less frequently, suicidal ideation have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms and if these occur, the patient should be advised to seek medical advice.

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.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Hepatic impairment

The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions of clinical importance have been identified. Finasteride is metabolized primarily via, but does not appear to affect significantly, the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4 will affect the plasma concentration of finasteride. However, based on established safety margins, any increase due to concomitant use of such inhibitors is unlikely to be of clinical significance.. Compounds which have been tested in man have included propranolol, digoxin, glibenclamide, warfarin, theophylline and phenazone 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 type II 5α-reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone (DHT), these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman.

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

The changes described above are expected pharmacological effects of Type II 5 α-reductase inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed in utero to finasteride are similar to those reported in male infants with a genetic deficiency of Type II 5 α-reductase. It is for these reasons that finasteride is contra-indicated in women who are or may potentially be pregnant.

No effects were seen in female offspring exposed *in utero* to any dose of finasteride

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 foetus (see 4.6 Fertility, pregnancy and lactation Pregnancy). Finasteride tablets are coated and will prevent 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 are no data to suggest that finasteride affects the ability to drive or to use machines.

4.8 Undesirable effects

The most frequent adverse reactions are impotence and decreased libido. These adverse reactions occur early in the course of therapy and resolve with continued treatment in the majority of patients.

The adverse reactions reported during clinical trials and/or post-marketing use with finasteride 5mg and/or finasteride at lower doses are listed in the table below.

Frequency of adverse reactions is determined as follows: 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), 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, angioedema (including swelling of the lips, tongue, throat and face)
Psychiatric disorders	
Common:	Decreased libido
Not known	Depression, decreased libido that continued after discontinuation of treatment, anxiety
Cardiac disorders	
Not known:	Palpitation
Hepatobiliary disorders	
Not known:	Increased hepatic enzymes
Skin and subcutaneous tissue disorders	
Uncommon:	Rash
Not known:	Pruritus, urticaria
Reproductive system and breast disorders	
Common:	Impotence
Uncommon:	Ejaculation disorder, breast tenderness, breast enlargement
Not known:	Testicular pain, haematospermia, sexual dysfunction(erectile dysfunction and ejaculation disorder) which may continue after discontinuation of

	treatment; male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.
Investigations	
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.

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 5 mg and 1147 (24.4%) men receiving placebo. In the finasteride 5 mg 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 5 mg group may be explained by a detection bias due to the effect of finasteride 5 mg 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). In most patients, a rapid decrease in PSA is seen within the first months of therapy, after which time PSA levels stabilise to a new baseline. The post-treatment baseline approximates 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 clinical interpretation see 'Special warnings and precautions for use', 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients have received single doses of finasteride up to 400 mg and multiple doses up to 80 mg/day for three months without adverse effects. No specific treatment of overdosage with finasteride is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Testosterone-5α-reductase-inhibitors

ATC-Code: G 04 CB 01

Mechanism of action

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 efficacy and safety

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 QUASJI-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 BPHwho were randomised to receive finasteride 5 mg/day, doxazosin 4 or 8 mg/day*, the combination of finasteride 5 mg/dayand doxazosin 4 or 8 mg/day*, or placebo. The primary endpoint was time to clinical progression of BPH, defined as a ≥4point 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 constitutedBPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression wasreduced 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

5.2 Pharmacokinetic properties

Absorption

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 Type II 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..*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 the elderly, the elimination rate of finasteride is somewhat decreased. Half-life is prolonged from a mean half-life of approximately six hours in men aged 18-60 years to eight 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 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.

There are no data available in patients with hepatic insufficiency.

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 foetuses. 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 foetal 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 foetuses. No other abnormalities were observed in male foetuses and no finasteride-related abnormalities were observed in female foetuses 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

Povidone K30

Magnesium stearate

Sodium laurilsulfate

Film-coating:

Opadry 03G20795 blue (Hypromellose (E464), Titanium dioxide (E171), Macrogol 6000, Macrogol 400, Indigo carmine aluminium lake (E132))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of the container

Blister packs PVC/PVDC/Aluminium: 10, 14, 15, 20, 28, 30, 50, 50x1, 56, 60, 98, 100, 100x1 tablets

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 UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/1024

9. DATE OF FIRST AUTHORISATION /RENEWAL OF AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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