

Finasteride 5 mg

Core Safety Profile

4.3 Contraindications

Finasteride is not indicated for use in women or children.

Finasteride is contraindicated in the following:

- Hypersensitivity to any component of this product
- Pregnancy - Use in women when they are or may potentially be pregnant (see 4.6 Pregnancy and lactation, Exposure to finasteride - risk to male fetus).

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.

Effects on 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 5 mg 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.

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.

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 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 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.

Pediatric use

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

Lactose

The tablet contains lactose monohydrate. Patients with any of the following genetic deficiencies should not take this drug: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Hepatic insufficiency

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.

4.6 Pregnancy and lactation

Pregnancy

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

Because of the ability of type II 5 α -reductase inhibitors to inhibit conversion of testosterone to dihydrotestosterone, these drugs, including 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 tablets of finasteride 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 (see 4.6 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.

Lactation

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 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 are listed in the table below.

Frequency of adverse reactions is determined as follows:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ 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.

System Organ Class	Frequency: adverse reaction
Immune system disorders	<i>Unknown</i> : hypersensitivity reactions including swelling of the lips and face
Psychiatric disorders	<i>Common</i> : decreased libido
Cardiac disorders	<i>Unknown</i> : palpitation
Hepatobiliary disorders	<i>Unknown</i> : increased hepatic enzymes
Skin and subcutaneous tissue disorders	<i>Uncommon</i> : rash <i>Unknown</i> : pruritus, urticaria
Reproductive system and breast disorders	<i>Common</i> : impotence <i>Uncommon</i> : ejaculation disorder, breast tenderness, breast enlargement <i>Unknown</i> : testicular pain
Investigations	<i>Common</i> : decreased volume of ejaculate

MAH proposes to include the following changes to section 4.8:

4.8 Undesirable effects

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

Psychiatric disorders:

Common: decreased libido

Unknown: depression

Reproductive system and breast disorders:

Common: impotence

Uncommon: ejaculation disorder, breast tenderness, breast enlargement

Unknown: testicular pain, erectile dysfunction that continued after discontinuation of treatment; male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

Assessor's comment: The proposed changes are not accepted see further in FAR. No changes in the CSP.

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

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 Special warnings and precautions for use).

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.