Sterifine® 5

Finasteride

FORMS AND PRESENTATION

Sterifine® 5: Film coated tablets: Box of 30.

COMPOSITION:

Sterifine® 5: Each film coated tablet contains Finasteride 5mg.

Excipients: lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hypromellose, titanium dioxide, FD&C blue, talc, iron oxide yellow.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Finasteride is a competitive inhibitor of human 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 (transurethral resection of the prostate (TURP) or prostatectomy) from 10/100 to 5/100. These reductions were associated with a 2-point improvement in QUASI-AUA (American Urological Association) 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 (titrated from 1 mg to 4 or 8 mg as tolerated over a 3-week period), the combination of Finasteride 5 mg/day and doxazosin 4 or 8 mg/day (titrated from 1 mg to 4 or 8 mg as tolerated over a 3-week period), 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.

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, feminisation 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 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 amount 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.

Pharmacokinetic Properties

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. 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 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 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.

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

INDICATIONS

Sterifine® 5 is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in patients with an enlarged prostate 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.

CONTRAINDICATIONS

− hypersensitivity to any component of this product

− women who are or may potentially be pregnant

− children.

PRECAUTIONS

General

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

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.

Digital rectal examination, as well as other evaluations for prostate cancer, should be carried out on patients with BPH prior to initiating therapy with Finasteride and periodically thereafter. Generally, when PSA assays are performed a baseline PSA >10 ng/ml 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. 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 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 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.
Excipients
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

PREGNANCY AND LACTATION

Pregnancy: Finasteride is contra-indicated in women who are or may potentially be pregnant.
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 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 foetus
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 foetus. 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 foetus 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.

DRUG INTERACTIONS

No clinically important drug interactions have been identified. Finasteride does not appear to significantly affect the cytochrome P450 linked drug metabolising enzyme system. Compounds which have been tested in man include propranolol, digoxin, glibenclamide, 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, H_2 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.

ADVERSE EFFECTS

Finasteride is well tolerated. In controlled clinical studies where patients received 5 mg of Finasteride over periods of up to four years, the following adverse reactions were considered possibly, probably or definitely drug-related and occurred with a frequency greater than placebo and greater than or equal to 1%: impotence, decreased libido, ejaculation disorder, decreased volume of ejaculate; breast enlargement, breast tenderness and rash. There was no evidence of increased adverse experiences with increased duration of treatment with Finasteride and the incidence of new drug-related sexual adverse experiences decreased with duration of treatment.
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%.
Other long-term data
In a 7 year placebo-controlled trial that enrolled 18,882 healthy men, of 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%) of men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs 237 (5.1%). Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The relationship between long-term use of Finasteride and tumours with Gleason scores of 7-10 is unknown.
Post Marketing Experience
The following additional adverse experiences have been reported in post-marketing experience:
− hypersensitivity reactions, including pruritus, urticaria and swelling of the lips and face
− testicular pain.
Laboratory test findings
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 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.
No other difference was observed in patients treated with placebo or Finasteride in standard laboratory tests.

DOSAGE AND ADMINISTRATION

The recommended adult dose is one 5 mg tablet daily, with or without food.
Sterifine® 5 can be administered alone or in combination with the alpha-blocker doxazosin.
Although early improvement in symptoms may be seen, treatment for at least six months may be necessary to assess whether a beneficial response has been achieved. Thereafter, treatment should be continued long term.
No dosage adjustment is required in the elderly or in patients with varying degrees of renal insufficiency (creatinine clearances as low as 9 ml/min).
There are no data available in patients with hepatic insufficiency.
Sterifine® 5 is contra-indicated in children.

OVERDOSAGE

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

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.
Date of revision: February 2014.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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