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APPROVED
Order of the Ministry of Protection Health of Ukraine _____
№ _____
Registration certificate № _____

INSTRUCTION for medical use of the drug PROSCAR® (PROSCAR®)

***Composition**: active substance: finasteride; 1 tablet contains finasteride 5 mg; excipients: lactose monohydrate; corn starch; sodium starch glycolate; iron oxide yellow (E 172); sodium docusate; microcrystalline cellulose; magnesium stearate. tablet shell: hypromellose, hydroxypropylcellulose with silicon dioxide, titanium dioxide (E 171), talc, indigo carmine aluminum varnish (E 132).*

Dosage form: Film-coated tablets.

Pharmacotherapeutic group: Means used in benign prostatic hypertrophy.

ATC code: G04C B01.

Clinical characteristics

Indication: Treatment and control of benign prostatic hyperplasia (BPH) in patients with enlarged prostate to:

—Reducing the size (regression) of the enlarged gland, improving the outflow of urine and reducing the symptoms associated with BPH;

—Reducing the risk of acute urinary retention and the need for surgery, including transurethroresection of the prostate and prostatectomy.

Contraindication

Hypersensitivity to finasteride or to any component of this drug. Proscar is not indicated for use in women and children.

Pregnancy: Use in women when they are or may be potentially pregnant (see section "Pregnancy or breast-feeding").

Method of application and dosage: The recommended dose is 1 tablet of 5 mg once a day during or regardless of meals. Proscar can be used as monotherapy in combination with the alpha-blocker doxazosin (see section "Pharmacological properties"). The duration of treatment is determined by the doctor individually. Although improvement in symptoms may be seen earlier, it is necessary to take at least six months to evaluate the effectiveness of the drug, after which it is necessary to continue treatment. No dose adjustment is required for elderly patients or for patients with renal insufficiency of varying severity (reduction of creatinine clearance to 9 ml / min). There are no data on the use of the drug in patients with impaired liver function. Do not use in children.

Adverse reactions

The most common side effects are impotence and decreased libido. These side effects occur at the beginning of therapy and occur with subsequent treatment in most patients. Adverse reactions reported in clinical trials and/or post-marketing experience are listed in the table below. The frequency of adverse reactions is defined as: very common (≥1 / 10), common (≥1 / 100 - <1/10), uncommon (≥1 / 1000 - <1/100), rare (≥1 / 10,000 - <1) / 1000), very rare (<1 / 10,000), not known (cannot be estimated from the

available data). The incidence of adverse reactions reported in post-marketing experience cannot be determined as spontaneous reports have been reported.

Systemic organs	Frequency of manifestations
From the immune system	Not known: hypersensitivity reactions including pruritus, urticaria and Quincke's edema (including swelling of the lips, tongue, throat and face)
From the psyche	Common: decreased libido Not known: decreased libido, which may continue after discontinuation of therapy, depression.
From the cardiac system	Not known: rapid heartbeat.
From the liver and biliary tract	Not known: elevated liver enzymes.
From the skin and subcutaneous tissues	Uncommon: rash. Not known: itching, urticaria.
From the reproductive system and mammary glands	Common: impotence. Uncommon: ejaculation disorder, breast tenderness and enlargement. Not known: testicular pain, erectile dysfunction, which may persist after cessation of treatment; male infertility and/or reversible sperm quality abnormalities (normalization or improvement in sperm quality has been reported after discontinuation of finasteride).
According to research	Common: reduced ejaculation.

In addition, breast cancer has been reported in clinical trials and in post-marketing experience in men taking finasteride. Any changes in breast tissue, such as swelling, pain, gynecomastia, or nipple discharge, should be reported to your doctor immediately. The MTOPS study compared finasteride, 5 mg / day (n = 768), doxazosin, 4 or 8 mg / day (n = 756), combination therapy with finasteride, 5 mg / day, and doxazosin, 4 or 8 mg / day (n = 768). 786), and placebo (n = 737). The safety and tolerability profile of combination therapy corresponded to the profiles of the individual components.

The incidence of ejaculation disorders in patients receiving combination therapy was comparable to the sum of the incidence of adverse reactions for the two monotherapies. In a seven-year placebo-controlled study involving 18,882 healthy men, of whom 9,060 received needle biopsy data available for analysis, prostate cancer was detected in 803 (18.4%) men receiving Proscar®, and 1,147 (24.4%) men who took placebo. In the Proscar® group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected by needle biopsy, compared with 237 (5.1%) men in the placebo group. Additional tests indicate that the increase in the prevalence of high-grade prostate cancer seen in the Proscar® group can be explained by the effect of Proscar® on prostate volume. Of the total number of prostate cancers diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2) cancer. There is no information on the association between long-term use of Proscar and tumors with Gleason scores of 7-10. Laboratory test data When evaluating laboratory tests for prostate-specific antigen (PSA), it should be borne in mind that PSA levels are reduced in patients taking Proscar. In most patients, a rapid decrease in PSA is observed during the first months of therapy, after which the PSA level stabilizes to a new initial level. The initial level after treatment is about half the value before treatment. Therefore, in most patients taking Proscar for six months or more, the PSA should be doubled compared to normal ranges in men who have not been treated. In standard laboratory tests, there were no other differences between patients receiving Proscar and patients receiving placebo.

Overdose

In patients receiving Proscar at a dose of up to 400 mg once and Proscar at a dose of up to 80 mg daily for 3 months, no adverse effects were observed. There are no specific recommendations for treatment of Proscar overdose®.

Use during pregnancy or breastfeeding

Use during pregnancy. Proscar® is contraindicated for pregnant women. Women who are potentially pregnant or pregnant should avoid contact with crushed Proscar tablets or those that have lost their integrity. There are data on the release of a small amount of finasteride from the semen of a patient taking finasteride 5 mg / day. It is not known whether a male fetus may be adversely affected by the fact that his mother was affected by the semen of a patient treated with finasteride. If the patient's sexual partner is or may be potentially pregnant, the patient is advised to prevent the effects of semen on the partner. Due to

the ability of type 2 alpha-reductase inhibitors to inhibit the conversion of testosterone to dihydrotestosterone, these drugs, including finasteride, may cause abnormal development of the external genitalia in the male fetus. Proscar tablets are coated, and this prevents contact with the active ingredient, provided that the tablets are not crushed and have not lost their integrity. Use during breastfeeding. Proscar is not prescribed to women. It is not known whether finasteride passes into breast milk.

Children

Proscar is contraindicated in children. Safety and efficacy in children have not been established.

Features of application

General measures: Careful monitoring of the possible development of obstructive uropathy in patients with a large residual urine volume and / or a sharp decrease in urine flow should be performed.

Effect on prostate-specific antigen (PSA) and diagnosis of prostate cancer To date, no favorable clinical effect of Proscar treatment has been shown in patients with prostate cancer. Patients with prostate adenoma and elevated PSA levels were observed in controlled clinical trials with multiple PSA determinations and prostate biopsy. In these studies, Proscar treatment did not affect the incidence of prostate cancer. The overall incidence of prostate cancer did not differ significantly between groups of patients receiving Proscar or placebo. It is recommended that patients be examined by rectal examination and other methods for prostate cancer before and periodically during treatment with Proscar. Serum PSA determination is also used to detect prostate cancer. In general, at baseline PSA levels above 10 ng / ml (Hybritech), the patient should be thoroughly examined, including, if necessary, a biopsy. At a PSA level of 4-10 ng / ml, further examination of the patient is recommended. There is a significant match in PSA levels in men who have prostate cancer and who do not have it. Therefore, in men with prostate adenoma, normal PSA values do not rule out prostate cancer, regardless of treatment with Proscar. A baseline PSA level below 4 ng / mL does not rule out prostate cancer. Proscar causes a reduction in serum PSA of approximately 50% in patients with prostate adenoma, even in the presence of prostate cancer. This reduction in serum PSA levels in patients with prostate adenoma treated with Proscar should be taken into account when assessing PSA levels, as this reduction does not rule out concomitant prostate cancer. This reduction is predictable across the range of PSA levels, although it may vary in individual patients. In most patients who receive Proscar for 6 months or more, the PSA should be doubled compared to normal in those not receiving treatment. This correction preserves the sensitivity and specificity of the PSA determination and supports its ability to detect prostate cancer. Any prolonged increase in PSA levels in a patient receiving finasteride 5 mg should be closely monitored to determine the cause, including non-compliance with the Proscar® regimen.

The effect of the drug on laboratory data

Effect on PSA level Serum PSA levels correlate with patient age and prostate volume, with prostate volume correlating with patient age. When assessing the laboratory parameters of PSA, it is necessary to take into account the fact that the level of PSA decreases during treatment with Proscar®. Most patients experience a rapid decrease in PSA during the first months of treatment, after which the PSA level stabilizes at a new level, which is approximately half of the baseline. Therefore, in typical patients receiving Proscar for 6 months or more, PSA values should be doubled compared to normal values in non-treatment recipients. Proscar® does not significantly reduce the percentage of free PSA (ratio of free PSA to total). The ratio of free and total PSA remains constant even under the influence of the drug Proscar®. It is not necessary to adjust the percentage of free PSA used to diagnose prostate cancer.

Breast cancer in men

Breast cancer has been reported in clinical trials and in the post-marketing setting in men taking finasteride 5 mg. Physicians should instruct their patients on the need to immediately report any changes in breast tissue, such as swelling, pain, gynecomastia, or nipple discharge.

Lactose

The drug contains lactose, so patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hepatic failure

The effect of hepatic insufficiency on the pharmacokinetics of finasteride has not been studied. Ability to influence the speed of reaction when driving a car and working with other mechanisms. Does not affect the ability to drive and use machines. Interaction with other medicinal products and other forms of interaction. No clinically significant interactions with other drugs were found. Proscar has no significant effect on the enzyme system that metabolizes cytochrome P450-related drugs. Although the risk of finasteride affecting the pharmacokinetics of other medicinal products is estimated to be low, it is likely that cytochrome P450 3A4 inhibitors and inducers will affect the plasma concentrations of finasteride. However, given the established safety data, any increase in finasteride concentrations due to concomitant use of cytochrome P450 3A4 inhibitors is unlikely to be of clinical significance. Compounds tested on humans include propranolol, digoxin, glyburide, warfarin, theophylline and antipyrine; no clinically significant interactions were found.

Pharmacological properties

Pharmacodynamics: Finasteride is a specific inhibitor of 5-alpha-reductase type II, an intracellular enzyme that converts testosterone to the more active androgen dihydrotestosterone (DHT). In BPH, its increase depends on the conversion of testosterone to DHT in prostate tissue. Finasteride is highly effective in reducing both circulating and intraprostatic DHT. Finasteride has no affinity for androgen receptors. In clinical trials in patients with moderate to severe BPH, enlarged prostate on digital rectal examination, and low residual urine volume, Proscar reduced the incidence of acute urinary retention from 7/100 to 3/100 over four years and the need for surgery (transurethroresection of the prostate and prostatectomy) from 10/100 to 5/100. This decrease was accompanied by a 2-point improvement in the QUASI-AUA symptom rating scale (range 0-34), a significant regression of prostate volume of approximately 20%, and a significant increase in urinary flow rate. The MTOPS (Medical Treatment of Prostatic Symptoms) study was a 4-6-year study of 3,047 men with symptomatic BPH who were randomized to finasteride, 5 mg / day, doxazosin, 4 or 8 mg / day, finasteride combinations, 5 mg / day, and doxazosin, 4 or 8 mg / day, or placebo. The primary endpoint was the time to clinical progression of BPH (defined as an increase from baseline of 4 or more points on the symptom rating scale, an episode of acute urinary retention associated with BPH and renal failure; recurrence of urinary tract infection or urosepsis, or urinary incontinence).). Compared with placebo, treatment with finasteride, doxazosin or a combination 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 cases (274 of 351) that accounted for BPH progression were confirmed by an increase of ≥ 4 points on the symptom rating scale; under the influence of treatment the risk of symptom progression was reduced by 30% (95% confidence interval 6-48%), 46% (95% confidence interval 25-60%) and 64% (95% confidence interval 48-75%), respectively, in the groups finasteride, doxazosin and the combination compared with placebo. Acute urinary retention was observed in 41 of 351 cases of BPH progression; under treatment, the risk of 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 with placebo. Only the finasteride and combination therapy groups had a significant difference from the placebo group.

Pharmacokinetics

In men, after a single oral dose of finasteride labeled with 14C carbon isotopes, 39% of the dose was excreted in the urine as metabolites (probably a small amount of unchanged finasteride was also excreted in the urine). 57% of the dose was excreted in the feces. Studies have also shown that the two metabolites of finasteride have a less pronounced inhibitory effect on 5-alpha-reductase. The bioavailability of finasteride when taken orally is approximately 80%. Food intake does not affect the bioavailability of the drug. The maximum concentration of finasteride in blood plasma is reached approximately in 2 hours after oral administration. Absorption of the drug from the gastrointestinal tract ends in 6-8 hours after ingestion. The half-life of fin-steroid in blood plasma averages 6 hours. Plasma protein binding is 93%. The systemic clearance is approximately 165 ml / min and the volume of distribution is 76.1 liters. In old age, the rate of excretion of finasteride decreases slightly. In men over 70 years of age, the half-life of finasteride is approximately 8 hours, while in persons aged 18 to 60 years - 6 hours. But this is not an indication to reduce the dose of the drug in the elderly. In patients with chronic renal failure (creatinine clearance 9 to 55 ml / min), there was no difference in the rate of excretion of a single dose of finasteride labeled with 14C carbon isotopes compared to healthy volunteers. Plasma protein binding was also not different in these patient groups. This is due to the fact that in patients with renal insufficiency, the proportion of finasteride metabolites, which under normal conditions is excreted in the urine, is excreted in the feces. This is confirmed by an increase in these patients with the amount of finasteride metabolites in the stool while reducing their concentration in the urine. Due to this, no dose adjustment of Proscar is required in patients with renal insufficiency not indicated for hemodialysis. There

are no data on the pharmacokinetics of the drug in patients with hepatic insufficiency. Finasteride crosses the blood-brain barrier. A small amount of finasteride was found in semen.

Pharmaceutical characteristics

Basic physical and chemical properties: pills in the shape of an apple, blue color

Packaging: 14 film-coated tablets in a blister. 1 or 2 blisters in a cardboard box.

Bulk products: MSD International GmbH (Puerto Rico Branch) Ltd., USA / MSD International GmbH (Puerto Rico Branch) LLC, United States. Primary packaging: Merck Sharp & Dohme Limited, United Kingdom. Secondary packaging, series release:

Merk Sharp & Dohme BV, The Netherlands.

Location. Road 2, Kilometer 60.3 Sabana Hoyos, Arecibo PR, 00688 USA / Road # 2, Kilometer 60.3 Sabana Hoyos, Arecibo PR, 00688 United States. Shotton Lane, Cramlington, Northumberland NE23 3JU, United Kingdom / Shotton Lane, Cramlington, Northumberland NE23 3JU, United Kingdom. Waarderweg 39, 2031 BN Haarlem, The Netherlands / Waarderweg 39, 2031 BN Haarlem, the Netherlands.

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