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Czechia State Institute for Drug Control
Aurovitas Finasteride Leaflet

Sp.zn.sukls252746 / 2019

SUMMARY OF PRODUCT

1. NAME OF THE MEDICINAL PRODUCT

Aurovitas Finasteride 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg finasteride. Excipient with known effect: contains 97.5 mg of lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet. Blue, round (7.6 mm diameter), biconvex, film-coated tablets with bevelled edges, debossed with "E" on one side and "61" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aurovitas Finasteride is indicated for the treatment and control of benign prostatic hyperplasia (BPH) in adult patients with an enlarged prostate to:

• Achieve regression of prostate enlargement, improve urine flow and alleviate BPH-related symptoms
• reduce the incidence of acute urinary retention and the need for surgery, including transurethral resection of the prostate (TURP) and prostatectomy.

4.2 Posology and method of administration Dosage Dosage in adults

The recommended dose is one 5 mg tablet daily (with or without food). Although relief of symptoms can be observed early, a minimum duration of treatment of 6 months is required to objectively assess the achievement of a satisfactory response to treatment.

Special patient groups: Elderly patients

No dose adjustment is required in elderly patients, although pharmacokinetic studies have shown a slight reduction in the elimination rate of finasteride in patients over 70 years of age.

Hepatic impairment

No data are available in patients with hepatic impairment (see section 4.4).
Renal impairment

No dose adjustment is required in patients with varying degrees of renal impairment (creatinine clearance reduced to 9 ml / min) as pharmacokinetic studies in patients with renal impairment did not show an effect on the elimination of finasteride. Finasteride has not been studied in hemodialysis patients.

Pediatric population

Aurovitas Finasteride is contraindicated in children. The safety and efficacy of finasteride in children have not been established.

Method of administration

Oral use only. The tablets should be swallowed whole and must not be divided or broken (see section 6.6). Aurovitas Finasteride can be administered alone or in combination with the alpha-blocker doxazosin (see section 5.1).

4.3 Contraindications Aurovitas Finasteride is not intended for use in women or children. Aurovitas Finasteride is contraindicated in the following cases:

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• pregnancy - women who are pregnant or may become pregnant (see section 4.6 Fertility, pregnancy and lactation. Finasteride exposure - risk to the male fetus).

4.4 Special warnings and precautions for use

In general

To avoid complications associated with obstruction, it is important to closely monitor patients with large residual urine volumes and / or significantly reduced urine flow. The possibility of surgery should also be considered.

Influence on prostate specific antigen (PSA) and prostate cancer detection:

No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride. Patients with benign prostatic hyperplasia (BPH) and elevated serum prostate specific antigen levels were monitored in controlled clinical trials using serial PSA measurements and prostate biopsies. In these BPH studies, finasteride was not shown to alter the rate of prostate cancer detection, and the overall incidence of prostate cancer did not differ statistically between patients treated with finasteride and placebo. Digital rectal examination and further examination for possible prostate cancer is recommended before and regularly after treatment with finasteride. Serum PSA assays are also used to detect prostate cancer. In general, an initial PSA value> 10 ng / ml (Hybritech) requires further monitoring and consideration of the biopsy; additional monitoring is recommended for PSA levels between 4 and 10 ng / ml. PSA levels overlap significantly in men with and without prostate cancer.

Therefore, in men with BPH, PSA values in the normal reference range do not rule out prostate cancer, regardless of finasteride treatment. An initial PSA value <4 ng / ml does not rule out prostate cancer. Finasteride reduces serum PSA levels in approximately 50% of patients with benign prostatic hyperplasia (BPH), including prostate cancer. This reduction in serum PSA levels in patients with benign prostatic hyperplasia treated with finasteride should be considered in the evaluation of PSA and does not rule out the co-occurrence of prostate cancer. This reduction can be expected across the range of PSA values, although it may vary from patient to patient.

Analysis of PSA in more than 3,000 patients in a double-blind, placebo-controlled, long-term efficacy and safety study [PLESS] for 4 years confirmed that in typical patients treated with finasteride for six months or more, PSA values should be doubled to it was possible to compare them with normal values in untreated men. This adjustmentpreserves the sensitivity and specificity of PSA assays and preserves the ability of this method to detect prostate cancer. Any persistent increase in PSA levels in patients treated with finasteride should be closely monitored and the possibility that the patient has stopped taking finasteride should be considered in the evaluation. The proportion of free PSA (ratio of free to total PSA) does not decrease significantly with finasteride treatment. The ratio of free to total PSA remains constant even under the influence of finasteride. If the proportion of free PSA is used to aid in the detection of prostate cancer, no adjustment is required. Interaction of the substance with laboratory tests Influence on PSA values Serum PSA levels correlate with patient age and prostate volume, and prostate volume correlates with patient age. When evaluating laboratory PSA values, the fact that PSA values in patients treated with finasteride should decrease should be taken into account. In most patients, we observe a significant decrease in PSA values in the first months of treatment, after which the PSA values stabilize at the new value. The post-treatment value corresponds to approximately half of the pre-treatment value. Therefore, in typical patients treated with finasteride for six months or more, PSA values should be doubled to allow comparison with the normal range of values in untreated men. (For clinical interpretation, see section 4.4: Special warnings and precautions for use.)

Impact on prostate specific antigen (PSA) and prostate cancer detection. Breast cancer in men During clinical trials and in the post-marketing setting, cases of breast cancer have been reported in men taking finasteride 5 mg. Physicians should instruct their patients to report any changes in breast tissue immediately, such as lumps, pain, gynecomastia, or nipple discharge. Pediatric population Aurovitas Finasteride is not indicated for use in children. Safety and effectiveness in children have not been established.

Hepatic impairment

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

Mood swings and depression

Mood swings, including depressed mood, depression and, rarely, suicidal ideation, have been reported in patients treated with finasteride 5 mg. Patients should be monitored for psychiatric symptoms and, if they do occur, patients should be advised to consult a physician.

Lactose

Aurovitas Finasteride 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 clinically significant drug interactions were identified. Finasteride is primarily metabolised by the cytochrome P450 3A4 system, but does not appear to significantly affect it. Although the estimated risk of affecting the pharmacokinetics of other drugs with

finasteride is small, cytochrome P450 3A4 inhibitors and inducers are likely to affect finasteride plasma concentrations. However, based on the safety margins identified, any increase due to concomitant use of these inhibitors is unlikely to be clinically relevant. Finasteride does not appear to significantly affect the drug-metabolizing cytochrome P450 enzymatic system. Substances that have been tested in humans include propranolol, digoxin, glibenclamide, warfarin, theophylline and phenazone, and no significant interactions have been identified.

4.6 Fertility, pregnancy and lactation

Aurovitas Finasteride is contraindicated in women who are pregnant or may become pregnant (see section 4.3). Due to the ability of 5α-reductase type II inhibitors to inhibit the conversion of testosterone to dihydrotestosterone, these agents, including finasteride, may cause external genitalia abnormalities in the male fetus when administered to pregnant women (see section 5.3). Finasteride exposure - risk to the male fetus. Women who are pregnant or may become pregnant should not touch crushed or broken finasteride tablets due to the possible absorption of finasteride and the consequent potential risk to the male fetus (see section 6.6). Finasteride tablets are coated, which prevents contact with the active substance during normal handling, provided the tablet is not broken or crushed. A small amount of finasteride was found in the semen of men given finasteride 5 mg daily.

It is not known whether exposure of a pregnant woman exposed to the semen of a patient treated with finasteride may adversely affect the male fetus. If the patient's sexual partner is pregnant or may become pregnant, the patient is advised to minimize the partner's contact with sperm. Fertility Long-term human fertility data are lacking, and specific studies in subfertile men have not been performed. Male patients who planned to father a child were initially excluded from clinical trials. Although animal studies did not show relevant adverse effects on fertility, data on infertility and / or poor sperm quality were obtained from spontaneous post-marketing reports.

According to some of these reports, patients had other risk factors that may have contributed to infertility. Adjustments or improvements in sperm quality have been reported after discontinuation of finasteride. Breast feeding Aurovitas Finasteride is not indicated for use by 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 common side effects are impotence and decreased libido. These side effects usually occur at the beginning of treatment and disappear in most patients with continued treatment. Adverse reactions reported during clinical trials and / or during the post-marketing period are listed in the table below. The frequency of adverse reactions is defined 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 the post-marketing period cannot be determined because they are reported from spontaneous reports.

Organ system class	**Frequency: side effects**
Examination	Common: ejaculate volume reduction
Immune system disorders	Not known: hypersensitivity reactions (including swelling of the lips, tongue, throat and face)
Psychiatric disorders	Common: decreased libido Not known: depression, decreased libido, which continues after treatment, anxiety
Heart disorders	Not known: palpitations
Hepatobiliary disorders	Not known: increase in liver enzymes
Skin and subcutaneous tissue disorders	Uncommon: rash Not known: pruritus, urticaria
Reproductive system and breast disorders	Common: impotence Uncommon: ejaculatory disorders, breast tenderness, breast enlargement Not known: testicular pain, sexual dysfunction (erectile dysfunction and ejaculatory disorders) which continues after treatment, male infertility and / or poor sperm quality.

	Adjustments or improvements in sperm quality have been reported after discontinuation of finasteride.

In addition, breast cancer has been reported in men in clinical trials and in the post-marketing setting (see section 4.4). Prostate Symptom Therapy (MTOPS): The MTOPS study compared finasteride 5 mg / day (n = 768), doxazosin 4 or 8 mg / day (n = 756), finasteride 5 mg / day and doxazosin 4 or 8 mg / day (n = 786), and placebo (n = 737).

The safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculatory dysfunction in combination therapy patients was comparable to the sum of the frequency of this adverse event with both monotherapies.

Additional information on long-term use In a placebo-controlled study lasting 7 years, which involved 18,882 healthy men, of whom 9,060 results from prostate puncture biopsy were available, prostate cancer was found in 803 (18.4%) men taking finasteride and 1,147 (24.4%) men taking placebo. In the finasteride group, puncture biopsy revealed a Gleason score of 7-10 in 280 (6.4%) men, compared to 237 (5.1%) men in the placebo group. Further analyzes suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride group can be explained by a bias in the survey due to the effect of finasteride on prostate volume. Of the total number of prostate cancer cases diagnosed in this study, approximately 98% were classified as intracapsular (clinical stage T1 or T2). The clinical significance of the relationship between long-term finasteride use and tumors with a Gleason score of 7-10 is unknown.

Breast cancer

The 4-6-year placebo-controlled study (MTOPS), which included 3,047 men, identified 4 cases of breast cancer in men receiving finasteride and no cases in men in the placebo group. During a 4-year placebo-controlled PLESS study of 3,040 men, 2 cases of breast cancer were identified in men receiving placebo, and no cases were found in men receiving finasteride. During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT), which included 18,882 men, one case of breast cancer was found in men receiving finasteride and one case in men receiving placebo. Breast cancer has been reported in men taking finasteride in the post-marketing setting. The link between long-term use of finasteride and breast cancer is currently unknown.

Laboratory test findings

When evaluating laboratory PSA values, the fact that PSA values in patients treated with finasteride should decrease should be taken into account (see section 4.4). Reporting of suspected adverse reactions Reporting suspected adverse reactions after marketing authorization is important. This allows you to continue to monitor the benefits and risks of the medicine. Healthcare professionals are asked to report suspected adverse reactions to: State Institute for Drug Control Šrobárova 48 100 41 Prague 10 website: www.sukl.cz/nahlasit-nezadouci-ucinek

4.9 Overdose

Patients did not show any side effects after single doses of finasteride up to 400 mg and repeated doses of 80 mg / day for three months. There is no known treatment for finasteride overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Testosterone-5-α-reductase inhibitors ATC code: G04CB01 Finasteride is a synthetic 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme 5 α-reductase type II. The enzyme converts testosterone to the more effective androgen - dihydrotestosterone (DHT). The prostate, and therefore the hyperplastic prostate tissue, is dependent on testosterone conversion and DHT due to its normal function and growth. Finasteride does not show affinity for androgen receptors. Clinical studies have shown a rapid reduction in serum DHT levels by 70%, leading to a reduction in prostate volume. After 3 months, prostate size decreases by approximately 20%, and shrinkage continues to approximately 27% reduction after 3 years. Significant reduction occurs in the periurethral area in the immediate vicinity of the urethra. Urodynamic measurements also confirmed a significant reduction in detrusor pressure as a consequence of reduced obstruction. Compared to pre-treatment, there was a significant improvement in maximal urine flow and symptoms after a few weeks. Differences in maximal urine flow between the treated group and the placebo group were observed after 4 months and improvement in symptoms was observed after 7 months. All monitored efficacy parameters remained unchanged during the three-year follow-up period. Effect of four years of finasteride treatment on the incidence of acute urinary retention, the need for surgery, the incidence of symptoms and prostate volume: Clinical studies in patients with mild to severe symptoms of BPH, enlarged prostate with digital rectal examination and low residual urine volumes have shown that finasteride reduced the incidence of acute urinary retention from 7/100 to 3/100 over four years and the need for surgery (TURP). - transurethral resection of the prostate or prostatectomy) from 10/100 to 5/100. These reductions are associated with a two-point improvement on the QUASI-AUA scale (range 0-34), a sustained reduction in prostate volume of approximately 20%, and a sustained increase in urine flow rate.

Drug therapy of prostate symptoms

Prostate symptom medication (MTOPS) testing was performed in a 4-6 year study of 3,047 men with symptomatic BPH who randomly received 5 mg finasteride daily, 4-8 mg doxazosin daily *, a combined dose of 5 mg finasteride daily, and 4- 8 mg doxazosin * daily or placebo. The primary endpoint of the study was time to clinical progression of BPH, defined as a ≥4-point increase in baseline symptom rating scale, acute urinary retention, BPH-associated renal insufficiency, recurrent urinary tract infections, or urosepsis or incontinence. Compared with placebo, treatment with finasteride, doxazosin, or combination therapy significantly reduced the risk of clinical progression of BPH by 34% (p = 0.002), 39% (p <0.001), and 67% (p <0.001). In most cases (274 of 351) where clinical progression of BPH occurred, a ≥4-point increase in symptom assessment was confirmed; the risk of symptom progression was reduced by 30 (95% CI 6 to 48%), 46 (95% CI 25 to 60%) and 64% (95% CI 48 to 75%) for finasteride, doxazosin and combination therapy. with placebo. Acute urinary retention occurred in 41 of 351 cases of BPH progression; the risk of acute urinary retention was reduced by 67 (p = 0.011), 31 (p = 0.296) and 79% (p = 0.001) for finasteride, doxazosin and combination therapy compared to placebo. A significant difference compared to placebo was observed only in finasteride and combination therapy groups. * Observed values from 1 mg to 4 mg or 8 mg, tolerated over a 3-week period In this study, the safety and tolerability profile of the combination treatment was essentially the same as for the active substances administered alone. However, adverse reactions related to the “nervous system” and the “urogenital system” were observed more frequently when the two active substances were administered in combination (see section 4.8).

5.2 Pharmacokinetic properties

Absorption: The oral bioavailability of finasteride is approximately 80%. Maximum plasma concentrations are reached approximately 2 hours after drug administration and absorption is complete in 6-8 hours.

Distribution: Protein binding is approximately 93%. Plasma clearance is approximately 165 ml / min (70-279 ml / min) and the volume of distribution is approximately 76 l (44-96 l). Accumulation of small amounts of finasteride was observed after repeated administration. At a daily dose of 5 mg, the lowest steady state concentration of finasteride was calculated to be 8-10 ng / ml and remained stable over time.

Biotransformation: Finasteride is metabolised in the liver. Finasteride has no significant effect on the cytochrome P450 enzyme system. Two metabolites have been identified that show little 5-reductase inhibitory effect.

Elimination: The mean half-life is 6 hours (4-12 hours) (in men> 70 years, 8 hours, range 6-15 hours). Following administration of radiolabelled finasteride, approximately 39% (32-46%) of the administered dose is excreted in the urine as metabolites. Virtually no non-metabolised finasteride was detected in urine. Approximately 57% (51-64%) of the total dose is excreted in the faeces. The presence of finasteride was detected in the cerebrospinal fluid of patients for 7-10 days, but it cannot be said that the product is selectively concentrated in the cerebrospinal fluid. Finasteride was also detected in the seminal fluid of patients given 5 mg / day. The amount of finasteride in the seminal fluid was 50 to 100 times lower than the dose of finasteride (5 mg), which did not affect DHT levels in adult men.

In patients with chronic renal insufficiency with a creatinine clearance in the range of 9-55 ml / min, the elimination of 14C-finasteride did not differ from that in healthy volunteers. Protein binding also did not differ between patients with renal impairment. The proportion of metabolites normally excreted in the urine was excreted in the faeces. Thus, faecal excretion appears to compensate for urinary metabolite excretion. No dose adjustment is required in non-dialysed patients with renal impairment.

5.3 Preclinical safety data

The oral LD50 of finasteride in male and female mice is approximately 500 mg / kg. Oral LD50 finasteride male and female rats is approximately 400 and 1000 mg / kg.

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies in male rats showed reduced prostate and seminal vesicle weights, decreased accessory gonadal excretion, and reduced fertility index (due to the primary pharmacological effect of finasteride). The clinical significance of these findings is unknown. As with other 5-α-reductase inhibitors, feminisation of male rat fetuses was observed after gestation during finasteride administration. Intravenous administration of finasteride to pregnant Rhesus monkeys at doses up to 800 ng / day throughout the embryonic and fetal development period did not result in abnormalities in male fetuses. This dose is approximately 60-120 times the estimated amount in the semen of a man who has taken 5 mg finasteride and to whom the woman could be exposed. Reproductive toxicity is probably due to inhibition of 5-α-reductase. If the difference in the sensitivity of the species-specific enzyme to finasteride inhibition is taken into account, this value will be the same 4 times higher than the actual pharmacological exposure. To confirm the relevance of the Rhesus monkey model to human fetal development, oral administration of finasteride was 2 mg / kg / day (systemic exposure (AUC) of monkeys was below or sperm) of pregnant monkeys causing external genitalia 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

Core: Lactose monohydrate Microcrystalline cellulose 101 Sodium carboxymethyl starch (type A) Pregelatinised maize starch Sodium salt of docusate Magnesium stearate Coating layer: Hyprolose Hypromellose 2910/6 Titanium dioxide (E171) Talc Indigo carmine aluminum lacquer (E132) Yellow iron oxide (E172)

6.2 Incompatibilities Not applicable.

6.3 Shelf life 4 years

6.4 Special precautions for storage Do not store above 25 ° C.

6.5 Druhobal and contents of the package PVC / PE / PVDC / Al blister. Pack sizes: 10, 20, 28, 30, 50, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Pregnant women or women who may become pregnant should not handle crushed or broken finasteride tablets, there is a potential for absorption and there is a potential consequent risk to the male fetus. Finasteride tablets are coated with a film that prevents contact with the active substance, provided that the tablets have not been broken or crushed. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Aurovitas, Ltd. s r.o. Karlovarská 77/12 161 00 Prague 6

8. REGISTRATION NUMBER

87/427/16-C

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

10/19/2016

10. DATE OF REVISION OF THE TEXT

9/10/2019