pharmaniaga®

AVORNA

0.5mg Soft Capsule

NAME OF THE MEDICINAL PRODUCT
AVORNA 0.5 mg Soft Capsule

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 0.5 mg of dutasteride.
Excipient with known effect: lecithin (may contain soya oil). For list of excipients, please refer at bottom of this leaflet.

PRODUCT DESCRIPTION
Capsule, soft.
An oblong, opaque and yellow soft gelatin capsule containing an oily and yellowish liquid.

PHARMACODYNAMICS

Pharmacotherapeutic group: testosterone-5-alpha-reductase inhibitors.
ATC code: G04C B02.

Mechanism of action
Dutasteride is a dual inhibitor of 5 alpha reductase. It inhibits both type 1 and type 2, 5 alpha reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

Effects on DHT/Testosterone
The maximum effect of daily doses of AVORNA on the reduction on DHT is dose-dependent and is observed within 1 to 2 weeks. After 1 week and 2 weeks of daily dosing of AVORNA® 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 0.5 mg of dutasteride daily, the median decrease in serum DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years. This is an expected consequence of 5 alphareductase inhibition and did not result in any known adverse events.

Effect on Prostate Volume
Significant reductions in prostate volume have been detected as early as one month after initiation of treatment and reductions continued through Month 24 ($p<0.001$). AVORNA led to a mean reduction of total prostate volume of 23.6% (from 54.9ml at baseline to 42.1ml) at Month 12 compared with a mean reduction of 0.5% (from 54.0ml to 53.7ml) in the placebo group. Significant ($p<0.001$) reductions also occurred in prostate transitional zone volume as early as one month continuing through Month 24, with a mean reduction in prostate transitional zone volume of 17.8% (from 26.8ml at baseline to 21.4ml) in the AVORNA group compared to a mean increase of 7.9% (from 26.8ml to 27.5ml) in the placebo group at Month 12. The reduction of the prostate volume seen during the first 2 years of double-blind treatment was maintained during an additional 2 years of open-label extension studies. Reduction of the size of the prostate leads to improvement of symptoms and a decreased risk for AUR and BPH-related surgery.

PHARMACOKINETICS

Absorption
Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours. The absolute bioavailability in man is approximately 60% relative to a 2 hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

Distribution
Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma proteins (>99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months. Steady state serum concentrations (Css) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

Metabolism
In vitro, dutasteride is metabolised by the human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolized by CYP1A2, CY2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The five human serum metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

Elimination
Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of drug-related material and 6 minor metabolites (less than 5% each).

Only trace amounts of unchanged dutasteride (less than 0.1% of the dose) are detected in human urine.

At therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks.

Serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Linearity/non-linearity
Dutasteride pharmacokinetics can be described as first order absorption process and two parallel elimination pathways, one saturable (concentration-dependent) and one non-saturable (concentration independent).

At low serum concentrations (less than 3 ng/mL), dutasteride is cleared rapidly by both the concentration-dependent and concentration-independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days.

At serum concentrations, greater than 3 ng/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with terminal half-life of 3 to 5 weeks. At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower clearance dominates and the total clearance is linear and concentration-independent.

Elderly
Dutasteride pharmacokinetics and pharmacodynamics were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. Exposure of dutasteride, represented by AUC and Cmax values, was not statistically different when comparing age groups. Half-life was not statistically different when comparing the 50 to 69 year old group to the greater than 70 years old group, which encompasses the age of most men with BPH. No differences in drug effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

Renal impairment
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment
The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied.

INDICATIONS

Monotherapy
AVORNA is indicated for the treatment and control of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related surgery.

Combination With Alpha-Blocker
AVORNA in combination with the alpha-blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

RECOMMENDED DOSAGE AND ADMINISTRATION

Route of Administration: Oral

Pharmaceutical form: Soft capsules.

Adult males (including elderly)

Capsules should be swallowed whole and not chewed or opened, as contact with the capsule contents may result in irritation of the oropharyngeal mucosa.

AVORNA may be taken with or without food.

The recommended dose of AVORNA is one capsule (0.5 mg) taken orally once a day

Although an improvement may be observed at an early stage, treatment for at least 6 months may be necessary in order to assess objectively whether a satisfactory response to the treatment can be achieved.

For the treatment of BPH, AVORNA can be administered alone or in combination with the alpha-blocker tamsulosin (0.4 mg).

Renal impairment
The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of dutasteride is contraindicated.

CONTRAINDICATIONS

AVORNA contraindicated in:
- Women and children and adolescents.
- Patients with hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, soya, peanut or any of the other excipients.
- Patients with severe hepatic impairment.

WARNINGS AND PRECAUTIONS

General
Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with AVORNA. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5α-reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

Blood donation
Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Prostate cancer
Men taking AVORNA should be regularly evaluated for prostate cancer risk including PSA testing.

Prostate specific antigen (PSA)
Serum prostate-specific antigen (PSA) concentration is an important component of the screening process to detect prostate cancer.

Dutasteride causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment.

Patients receiving AVORNA should have a new PSA baseline established after 6 months of treatment with AVORNA. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on AVORNA may signal the presence of prostate cancer or non-compliance to therapy with AVORNA and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-ARI. In the interpretation of a PSA value for a patient taking AVORNA, previous PSA values should be sought for comparison.

Treatment with AVORNA does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.

Total serum PSA levels return to baseline within 6 months of discontinuing treatment.

The ratio of free to total PSA remains constant even under the influence of AVORNA. If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men undergoing AVORNA therapy, no adjustment to its value is necessary.

Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients prior to initiating therapy with AVORNA and periodically thereafter.

Cardiovascular adverse events
The incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than not taking the combination. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established.

Breast cancer
There have been rare reports of male breast cancer reported in men taking dutasteride. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-ARIs. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Leaking capsules
Dutasteride is absorbed through the skin, therefore women, children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules the contact area should be washed immediately with soap and water.

Hepatic impairment
The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride to patients with liver disease.

Increased Risk of High-Grade Prostate Cancer
In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).

5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

INTERACTIONS WITH OTHER MEDICAMENTS

In vitro drug metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4.

Data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37%) and diltiazem (44%). In contrast no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride.

A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10 times the recommended dose has been given to patients for up to six months); therefore no dose adjustment is necessary.

Dutasteride is not metabolized by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6, and CYP2D6.

Dutasteride neither inhibits human cytochrome P450 drug-metabolizing enzymes in vitro nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A.

Dutasteride does not displace warfarin, diazepam, acenocoumorol, phenprocoumon, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant pharmacokinetic or pharmacodynamic interactions have been observed.

Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

PREGNANCY AND LACTATION

Fertility
The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

Pregnancy
Dutasteride is contraindicated for use by women. Dutasteride has not been studied in women because preclinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male foetus carried by a woman exposed to dutasteride.

Lactation
It is not known whether dutasteride is excreted in human milk.

SIDE EFFECTS

Dutasteride Monotherapy for BPH
The most common adverse reactions reported in subjects receiving dutasteride were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders.

Dutasteride and Tamsulosin Combination Therapy for BPH
The most common adverse reactions reported in subjects receiving combination therapy (dutasteride plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness.

Immune system disorders
Very rare: Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.

Psychiatric disorders
Very rare: Depressed mood

Skin and subcutaneous tissue disorders
Rare: Alopecia (primarily body hair loss), hypertrichosis

Reproductive system and breast disorders
Very rare: Testicular pain and testicular swelling

SYMPTOMS AND TREATMENT OF OVERDOSE

There is no specific antidote for dutasteride, therefore, in suspected overdosage symptomatic and supportive treatment should be given as appropriate.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on the pharmacokinetics and pharmacodynamic properties of dutasteride, treatment with dutasteride would not be expected to interfere with the ability to drive or operate machinery.

INSTRUCTION OF USE

The capsules should be swallowed whole and not chewed or opened as contact with the capsule contents may result in irritation of the oropharyngeal mucosa. The capsules may be taken with or without food.

Dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. Women who are pregnant or may be pregnant should not handle Dutasteride because of the possibility of absorption of dutasteride and the potential risk of a foetal anomaly to a male foetus.

SHELF LIFE

36 months.

STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from light and moisture.

DOSAGE FORMS AND PACKAGING AVAILABLE

30 soft capsules packed in aluminium/PVC-PVDC white opaque blisters.

LIST OF EXCIPIENTS

Capsule contents: Glycerol Monocaprylocaprate (type 1), Butylhydroxytoluene

Capsule shell: Bovine Gelatin, Glycerol, Titanium dioxide (E171), Yellow Iron Oxide (E172), Medium Chain Triglycerides and Lecithin (may contain soya oil).

MANUFACTURER

Cyndea Pharma S.L.
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PRODUCT REGISTRATION HOLDER

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REVISION DATE

20 November 2024