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pharmaniaga®

AVORNA-DUO

0.5 mg/0.4 mg
Hard Capsules
dutasteride/tamsulosin hydrochloride

1. NAME OF THE MEDICINAL PRODUCT
AVORNA-DUO 0.5mg/0.4mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 0.5mg Dutasteride and 0.4mg Tamsulosin hydrochloride (equivalent to 0.367mg Tamsulosin).
Excipients with known effect: Each capsule contains lecithin (which may contain soya oil) and sunset yellow FCF (E 110). Each capsule contains ≤ 0.1 mg sunset yellow FCF. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsules.
Orange cap and brown body hard capsules containing white to off-white pellets and one yellow soft gelatin capsule with an oily and yellowish liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications
AVORNA-DUO is indicated as combination therapy for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).
AVORNA-DUO reduces the risk of acute urinary retention and the need for surgery in patients with moderate to severe symptoms of BPH.

4.2. Posology and method of administration
Patients >21 years old (including elderly patients)
The recommended dose of AVORNA-DUO is one capsule daily (0.5 mg / 0.4 mg).
AVORNA-DUO must always be taken with a glass of water, up to 30 minutes after a meal. It must never be taken on an empty stomach. Ideally it should be taken at the same time of the day (this means with the same meal).
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.

Special dosage instructions
Elderly patients:
No age-related dose adjustment is required.
Renal impairment
There is no experience available in patients with renal impairment. AVORNA-DUO should therefore be used with caution especially in patients with severe renal impairment (creatinine clearance <10ml/ min).
Hepatic impairment
There is no experience available in patients with hepatic impairment. AVORNA-DUO should be used with caution in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of AVORNA-DUO is contraindicated.
Patients ≤21 years old:
AVORNA-DUO is not indicated in patients ≤21 years old.

Route of Administration
Oral

4.3. Contraindications
- patients with a history of orthostatic hypotension.
- severe hepatic impairment.
- women, patients ≤21 years old.
- hypersensitivity to tamsulosin, dutasteride, other ingredients of the product or to other 5α-reductase inhibitors.

4.4. Special warnings and precautions for use
Prior to initiating treatment with AVORNA-DUO the patient should be examined to rule out other causes of the symptoms.
AVORNA-DUO should only be prescribed after a careful benefit/risk assessment due to the risk of adverse events from both active components, and after careful consideration of alternative treatment options (e.g. monotherapies).
Patients with large residual urinary volume and/or severely impaired urine flow should be monitored carefully for acute or chronic urinary retention.
As the active principle dutasteride is absorbed through the skin, contact with leaking capsules should be avoided. In the event of contact with leaking capsules the area affected should be washed thoroughly with soap and water at once. Women should not handle crushed or broken AVORNA-DUO capsules if they are pregnant or could become pregnant, due to the possibility of absorption of dutasteride and the possible risk to a male foetus.

Effects on prostate-specific antigen (PSA) and the detection of prostate cancers

Before initiating treatment with AVORNA-DUO tests to rule out prostate cancer including a digital rectal examination should be carried out. These tests should be repeated at regular intervals during the treatment.
The PSA serum level is an important parameter for early detection of prostate cancer. Treatment with AVORNA-DUO leads to an average reduction of 50% in PSA serum levels within 6 months (with great inter-individual fluctuations, standard deviation 30%). This is why PSA levels within the normal range in patients taking AVORNA-DUO do not rule out prostate cancer.
For this reason, after six months of treatment with AVORNA-DUO, PSA levels must be assessed again and the result of this measurement used as the baseline value for future measurements. Any confirmed rise in PSA levels compared to the lowest value determined during treatment with AVORNA-DUO may indicate the presence of prostate cancer (particularly high grade tumour) or lack of compliance and must therefore be evaluated carefully, even if values are still within the normal range for men who have not been treated with 5α-reductase inhibitors. A comparison with previous PSA values should be used to interpret the PSA value in patients treated with dutasteride.
After discontinuation of the treatment the PSA levels return to baseline values within 6 months.
The ratio of free to total PSA remains unchanged by AVORNA-DUO. If the doctor uses the percentage of free PSA as a marker to detect prostate cancer, no adjustment of the value is necessary during treatment with AVORNA-DUO.

Breast cancer in men
Data on a possible relationship between long-term therapy with dutasteride and the occurrence of breast cancer in men are currently inadequate. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

Hypotension
During treatment with an adrenergic alpha-1 receptor blocker such as tamsulosin orthostatic hypotension may occur which in rare cases can result in syncope. Caution is advised in particular in patients who exhibited an excessive haemodynamic reaction during previous treatment with an alpha-1 receptor blocker and in patients receiving antihypertensive therapy. In theory, when tamsulosin hydrochloride is co- administered with anaesthetics, PDE5 inhibitors or other adrenergic alpha-1 receptor blockers, there is a risk of potentiation of hypotensive effects. AVORNA-DUO must not therefore be used in combination with other adrenergic alpha-1 receptor blockers, and should only be used with caution in combination with PDE5 inhibitors.
Patients beginning treatment with AVORNA-DUO should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness) until the symptoms have resolved.

Cardiac failure under combined therapy with tamsulosin
Cases of (acute or chronic) cardiac failure under combined therapy with dutasteride and an alpha blocker (mainly tamsulosin) were observed more frequently than under a monotherapy with dutasteride or an alpha blocker (incidence under dutasteride 0.1%, under alpha blocker 0.2%, under combined therapy 0.6%). However, there was no difference between the three treatment groups for all of the undesirable effects in the cardiovascular system. Up until now there have been no grounds to suspect a causal connection between the medication and the manifestation of cardiac failure, especially since the majority of the patients affected presented predisposing illnesses such as arterial hypertonia or coronary heart disease.
In some cases the symptoms of heart failure did not occur until after more than one year of treatment.
Caution is advised in patients with coronary heart disease owing to the possible antihypertensive effects of tamsulosin (see below).

Intraoperative floppy iris syndrome
Intraoperative floppy iris syndrome (IFIS) has been observed during ophthalmological interventions (cataract and glaucoma surgery) in some patients treated with adrenergic alpha-1 receptor blockers, such as tamsulosin. IFIS is characterised by a flaccid iris, progressive intraoperative miosis despite premedication with standard mydriatics, and potential prolapse of the iris towards the incisions for phacoemulsification. IFIS may increase the risk of intraoperative and postoperative ophthalmological complications, and the surgeon should be prepared, if necessary, to adjust his surgical techniques accordingly.

It is recommended that treatment with tamsulosin is not initiated in patients who are about to undergo eye surgery. However, it has not been proven that discontinuation of tamsulosin 1-2 weeks prior to the intervention is beneficial. There have been some reports on IFIS in patients who discontinued tamsulosin some time prior to the operation.

Effects on the reproductive system
The relevance of the effects of dutasteride on semen characteristics for an individual patient's fertility is not known.
The effects of Tamsulosin hydrochloride on sperm count or function have not been examined.
In the case of combined administration of dutasteride and tamsulosin there was an increased incidence of undesirable effects in the organ system "reproductive system and breast", particularly at the start of the treatment (i.e. during the first 6-12 months) compared to therapy with dutasteride or tamsulosin alone.

Hepatic impairment
The effects of hepatic impairment on the pharmacokinetics of dutasteride have not been investigated. As dutasteride undergoes extensive metabolism and has a half- life of 3-5 weeks, AVORNA-DUO should be used with caution in patients with mild to moderate hepatic impairment (see section 4.2 and 4.3). Since also for tamsulosin there are no data regarding severe hepatic impairment available, AVORNA-DUO is contraindicated for severe liver impairment.

CYP3A4 inhibitors
Co-administration of tamsulosin and CYP3A4 inhibitors may increase tamsulosin exposure. In particular, there is a risk for significantly increased tamsulosin exposure in the case of CYP2D6 slow metabolisers who are being treated concurrently with potent CYP3A4 inhibitors. As polymorphism for CYP2D6 is generally unknown outside clinical studies, AVORNA-DUO should basically not be co- administered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir).

AVORNA-DUO should only be co-administered with caution with moderate CYP3A4 inhibitors (e.g. erythromycin, fluconazole, verapamil, diltiazem). This applies in particular if the patient is being concurrently treated with a potent or moderate CYP2D6 inhibitor (such as paroxetine) or if concurrent treatment is with a CYP3A4 inhibitor that also inhibits CYP2D6 (such as amiodarone, cimetidine, imatinib).

Renal impairment:
The effects of renal impairment on the pharmacokinetics of tamsulosin have not been investigated in patients with creatinine clearance <10 ml/min. AVORNA-DUO should therefore be used with caution in such patients. For dutasteride no pharmacokinetic data are available in patients with impaired renal function. Due to the minimal renal elimination, there is no meaningful impact expected.

Swallowing disorders
AVORNA-DUO has not been studied in patients with swallowing disorders (e.g. stenosing oesophageal changes or neurological disorders accompanied by impaired oesophageal motility). Caution is therefore advised in such patients.

Discontinuation of AVORNA-DUO
On discontinuing AVORNA-DUO the prostate can go back to the size it was prior to the treatment. Patients should therefore be suitably monitored for the recurrence of symptomatic BPH.

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.

Prostate cancer (in particular high grade tumours)
Based on reported data, studies in men at increased risk of prostate cancer revealed a higher incidence of Gleason 8 - 10 prostate cancers in men treat with 5α-reductase inhibitors (dutasteride or finasteride) compared to placebo. The relationship between 5α-reductase inhibitors and higher grade prostate cancer is not clear yet. Men taking AVORNA-DUO should be regularly evaluated for the manifestation of prostate cancer, including PSA testing.

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.

Excipients
This medicinal product contains the colouring agent sunset yellow (E-110), which may cause allergic reactions.

This medicinal product contains lecithin derived from soya oil. If you are allergic to peanut or soya, do not use this medicinal product.

4.5. Interactions with other medicinal products and other forms of interaction
There have been no drug interaction studies for AVORNA-DUO. The following statements reflect the information available on the individual components.

Pharmacokinetic interactions
Interactions with CYP450 enzyme system

Dutasteride
Dutasteride is metabolized by CYP3A4. A reduction in clearance by concomitant administration of CYP3A4 inhibitors is regarded as clinically irrelevant in view of the wide therapeutic window. In vitro, dutasteride is not metabolised by CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP2C8, CYP2C9, CYP2C19 and CYP2B6. Under in vitro conditions dutasteride has no inhibitory effect on cytochrome P450 enzymes.

Tamsulosin
Concomitant administration of tamsulosin with CYP3A4 or CYP2D6 enzyme inhibitors may lead to increased tamsulosin exposure. Concomitant administration of ketoconazole (a potent CYP3A4 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin by a factor of 2.2 and 2.8 respectively.
Concomitant administration of paroxetine (a potent CYP2D6 inhibitor) caused an increase of the C_{max} and AUC of tamsulosin by a factor of 1.3 and 1.6 respectively. The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitors with tamsulosin have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure.

Interactions with oral anticoagulants
Dutasteride
Dutasteride did not show any interaction with the plasma protein binding of warfarin, acenocoumarol or phenprocoumon in vitro.

Tamsulosin
No study has been conducted on interactions between tamsulosin hydrochloride and warfarin. Tamsulosin has no effect on the pharmacokinetics or efficacy of acenocoumarol in healthy subject. The effect of acenocoumarol on the pharmacokinetics of tamsulosin has not been investigated. There are no interaction studies with phenprocoumon. The INR values of patients on oral anticoagulation therapy should be closely monitored for 2-3 months when starting or stopping treatment with AVORNA-DUO.

Other pharmacokinetic interactions
Dutasteride
No clinically significant pharmacokinetic or pharmacodynamic interactions have been observed between dutasteride and tamsulosin, terazosin, warfarin, digoxin and cholestyramine.
In vitro, dutasteride did not displace diazepam or phenytoin from plasma protein binding and in turn was not displaced by them either.

Tamsulosin
Concomitant administration of tamsulosin hydrochloride and furosemide produced an 11-12% reduction in the C_{max} and AUC of tamsulosin hydrochloride; however these changes are clinically irrelevant and no dose adjustment is necessary.
Tamsulosin had no effect on the pharmacokinetics of atenolol, digoxin, enalapril, nifedipine or theophylline.

Pharmacodynamic interactions
Tamsulosin
Based on published data, studies on hypertonic patients whose blood pressure was stable with atenolol,enalapril or nifedipine, tamsulosin did not have a revelant effect on blood pressure compared to placebo.

4.6. Fertility, pregnancy and lactation
AVORNA-DUO is contraindicated in women.

No studies have been conducted with AVORNA-DUO to investigate the effect on pregnancy and lactation. The following statements reflect the information available on the individual components.

Pregnancy
5α-reductase inhibitors can inhibit the development of the external genitalia of male foetuses.
As dutasteride is absorbed through the skin, contact (especially with leaking capsules) should be avoided during pregnancy.
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 dutasteride.

Breast-feeding
It is not known whether dutasteride or tamsulosin hydrochloride are excreted in human breast milk.

Fertility
Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The

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possibility of reduced male fertility cannot be excluded.
Effects of Tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

4.7. Effects on ability to drive and use machine
The effect of AVORNA-DUO on the ability to perform tasks that require judgement, motor or cognitive skills have not been conducted. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension (such as dizziness) and visual disturbances when taking AVORNA-DUO that could impair the ability to drive and to use machines.

4.8. Undesirable effects
The most common undesirable effects during combined administration of Dutasteride and Tamsulosin hydrochloride related to the organ system "Reproductive system and breast". These undesirable effects were observed more frequently with the combination therapy than with the respective monotherapies and in each case were more frequent in the first year of treatment than in the subsequent years of treatment. The undesirable effects, which were observed either during one of the two monotherapies or in the co-administration study, are listed below by organ system and frequency.

Neoplasms	
Unknown:	Breast cancer in men
Immune system disorders	
Uncommon:	Rash, pruritus, urticaria
Rare:	Angioedema
Very rare:	Stevens-Johnson syndrome
Psychiatric disorders	
Common:	Decreased libido
Very rare:	Depressive mood
Nervous system disorders	
Common:	Dizziness
Rare:	Syncope
Eyes	
Unknown:	Blurred vision, visual disturbances

Following market launch there have also been reports of a relationship between the occurrence of what is known as Intraoperative Floppy Iris Syndrome (IFIS) during cataract and glaucoma surgery and treatment tamsulosin.

Cardiovascular disorders	
Uncommon:	Palpitations, orthostatic hypotension
Unknown:	Tachycardia, arrhythmias (e.g. atrial fibrillation)
Respiratory disorders	
Uncommon:	Rhinitis
Unknown:	Epistaxis, dyspnoea
Gastrointestinal disorders	
Uncommon:	Nausea, constipation, diarrhoea, vomiting, dry mouth
Skin and subcutaneous tissue disorders	
Unknown:	Exfoliative dermatitis, erythema multiforme
Reproductive system and breast disorders	
Common:	Impotence, ejaculation disorders (such as retrograde ejaculation), gynaecomastia, breast tenderness.
Very rare:	Priapism, testicular pain and testicular swelling
Unknown:	Persistent sexual dysfunction (such as impotence, ejaculation disorders and decreased libido) even after discontinuation of therapy
General disorders	
Uncommon:	Asthenia

4.9. Overdose
No data are available with regard to overdosage with AVORNA-DUO. The following statements reflect the information available on the individual components.

Dutasteride
There is no specific antidote for dutasteride. Therefore, if an overdose is suspected appropriate symptomatic treatment should be initiated.

Tamsulosin
Cases of acute overdose with 5mg tamsulosin have been reported. Acute hypotension (systolic blood pressure 70 mmHg), vomiting and diarrhoea were observed in these patients.
In cases of acute hypotension occurring after overdose with tamsulosin hydrochloride cardiovascular support should be given. Normalisation of blood pressure and heart rate may be accomplished by lying the patient down. If this is inadequate, volume expanders and if necessary vasopressors can then be administered. Since tamsulosin exhibits strong plasma protein binding, dialysis is unlikely to be of benefit in removing tamsulosin from the body. Vomiting may be induced to reduce absorption. If a large dose has been taken, administration of activated charcoal and osmotic laxatives may be useful.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52

Mechanism of action:
AVORNA-DUO is a combination of two drugs with complementary mechanisms of action to improve symptoms in patients with BPH: dutasteride, a dual 5α-reductase inhibitor (5-ARI) and tamsulosin hydrochloride, an antagonist of α_{1a}-adrenoreceptors.

Dutasteride
Dutasteride inhibits the Type 1 and 2 5α-reductase isoenzymes which are responsible for the conversion of testosterone to 5α-dihydrotestosterone (DHT) and therefore causes a fall in the DHT level in the circulation and in the prostate. DHT is the main androgen responsible for hyperplasia of the glandular prostate tissue.
Dutasteride reduces the size of the prostate, relieves the symptoms, improves urine flow and reduces the risk of acute urinary retention and the need for surgery.

Tamsulosin
Tamsulosin is a selective α1-adrenoreceptor blocker for the symptomatic treatment of functional symptoms of benign prostatic hyperplasia. It binds selectively and competitively to postsynaptic α1-adrenoreceptors (mainly the alpha$_{1a}$ subtype –approximately 75% of the α1-receptors in the prostate are of the α_{1a} subtype) responsible for contraction of the smooth muscle of the prostate and urethra. Tamsulosin thereby reduces smooth muscle tension in the prostate and urethra. This increases maximum urinary flow rate and reduces urinary tract obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.

Effects on DHT/testosterone:
Based on published data, the peak effect of dutasteride in the sense of reduction of DHT is dose-dependent and occurs within 1-2 weeks. After taking dutasteride (0.5 mg/day) for one or two weeks, the mean DHT concentrations in the serum were reduced by 85% and 90% respectively, after one year by 94% and after 2 years by 93%. After discontinuation of treatment the DHT serum concentrations associated with the clinical effects return to the baseline values within about 4 months.

The mean rise in the serum testosterone level was 19% after both one and two years. The testosterone concentrations fluctuated within the normal physiological range.

Safety Pharmacodynamics
Adrenergic alpha-1 receptor blockers can reduce blood pressure by lowering peripheral resistance.

5.2. Pharmacokinetic properties

Absorption:
Dutasteride
After oral administration, the peak serum concentration of dutasteride is attained within 1-3 hours. Absolute bioavailability compared with a 2-hour intravenous infusion is approximately 60%.

Tamsulosin
Tamsulosin hydrochloride is absorbed from the intestine and is almost completely available. Public data indicates after a single dose following a meal, tamsulosin plasma concentrations reach their peak after 6 hours.
Tamsulosin hydrochloride has linear absorption kinetics, with achievement of steady state concentrations by about the fifth day of once-a-day dosing. The rate of absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking tamsulosin hydrochloride 30 minutes after the same meal each day.
Tamsulosin plasma levels exhibit considerable inter-individual variability with both single and multiple dosing.

Distribution:
Dutasteride
Dutasteride has a large volume of distribution (300-500 l) and is highly plasma protein bound (> 99.5%; to albumin and α1-acid glycoprotein). Based on available data, the steady-state serum concentration (C_{ss}) of approximately 40 ng/ml at a dose of 0.5 mg dutasteride a day is achieved after 6 months. After 1 and 3 months the dutasteride serum levels reach 65% and about 90% respectively of the steady-state concentration. The steady-state concentration is also reached in seminal fluid after 6 months.
After administration for 12 months the dutasteride concentration in seminal fluid was on average 3.4 ng/ml (range 0.4-14 ng/ml), i.e. on average 11.5% of the serum level.

Tamsulosin
The volume of distribution of tamsulosin hydrochloride is low (approximately 0.2l/kg). Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily α-1 acid glycoprotein (AAG).

Metabolism:
Dutasteride
Dutasteride undergoes extensive metabolism. It is mainly hydroxylated and dehydrogenated to inactive metabolites. There are 4 major metabolites and 6 subsidiary metabolites. Hydroxylation takes place in vitro via CYP3A4.

Tamsulosin
Tamsulosin hydrochloride is extensively metabolised slowly by cytochrome P450 enzymes in the liver. Available data indicate that CYP3A4 and CYP2D6, and to a minor extent some other CYP isoenzymes, are involved in the metabolism of tamsulosin. However, the majority is present in the plasma in the form of the unchanged active ingredient. None of the metabolites is more active or more toxic than the parent substance. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Elimination:
Dutasteride
5.4% of the dose administered is excreted as unchanged dutasteride in the faeces, and the rest in the form of metabolites. Only traces of the unchanged substance (less than 0.1% of the dose) can be detected in the urine.
Dutasteride clearance is low. The elimination half-life is 3-5 weeks.

Tamsulosin
Following oral administration of tamsulosin in the form of modified release capsules, the apparent elimination half life in the fed state after a single dose is approximately 10 hours and in the steady state is approximately 13 hours. Approximately 10% of the substance is excreted unchanged in urine.

Kinetics of special patient populations
No pharmacokinetic studies have been conducted with AVORNA-DUO on special patient populations. The following statements reflect the information available on the individual components.

Elderly:
Dutasteride
In the age groups >50-65 years and >70 years there were no statistically significant differences in pharmacokinetics.

Tamsulosin
Findings indicate that overall exposure is approximately 40% increased in patients aged 55-75 years compared with young males.

Renal impairment:
Dutasteride
The effects of renal impairment on the pharmacokinetics of dutasteride have not been investigated. As less than 0.1% of the dose is excreted in the urine, no effect on the serum levels is to be expected.

Tamsulosin
No clinically relevant changes in the pharmacokinetics of tamsulosin were observed in patients with mild to moderate ($30 \leq CL_{cr} < 70$ mL/min/1.73m^2) or moderate to severe ($10 \leq CL_{cr} < 30$ mL/min/1.73m^2) renal impairment compared with subjects with normal renal function. However, patients with terminal renal disease ($CL_{cr} < 10$ mL/min/1.73m^2) have not been studied.

Hepatic impairment:
Dutasteride
The effects of hepatic impairment on the pharmacokinetics of dutasteride have not been investigated.

Tamsulosin
In patients with mild to moderate hepatic dysfunction (Child-Pugh classification: Grades A and B), no clinically relevant changes in the pharmacokinetics of tamsulosin hydrochloride were observed. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction (Child-Pugh C).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hard Capsule Shell:
Hypromellose, Potassium Chloride, Carrageenan, Titanium Dioxide, Sunset Yellow, Red Iron Oxide

Dutasteride 0.5mg Soft Capsule:
Glycerol monocaprylocaprate, Butylhydroxytoluene, Gelatin, Glycerol, Titanium Dioxide, Yellow Iron Oxide, Triglycerides, Lecithin (soya)

Tamsulosin 0.4mg Pellet:
Microcrystalline Cellulose, Magnesium Stearate, Methacrylic acid-Ethyl acrylate copolymer, Sodium Hydroxide, Triacetin, Purified Talc, Titanium Dioxide, Talc

6.2. Shelf life
Please refer to the expiry date on the product labels.

6.3. Special precautions for storage
Store below 30°C. Protect from light and moisture.

6.4. Nature and contents of containers
Alu/Alu blister of 3 x 10's packed in the outer carton.
Alu-Alu blister of 5 x 6's packed in the outer carton.

6.5. Special precautions for disposal and other handling
No special requirement.

7. MANUFACTURER

Manufactured by:
SAG MANUFACTURING, S.L.U.
Carretera Nacional 1 Km 36, San
Agustin del Guadalix, 28750 Madrid
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