Dutamsuvitae

(Dutasteride / Tamsulosin hydrochloride 0.5 mg/0.4 mg Hard capsules)

Name and strength of active substance
Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules

Product Description
Dutamsuvitae (Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules) are 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.

Pharmacodynamics
Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists, ATC code: G04CA52
Mechanism of action:
Dutamsuvitae 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 α1a-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 alpha1a subtype – approximately 75% of the α1-receptors in the prostate are of the α1a 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:
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.

Pharmacokinetics
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 approx. 60%.

Tamsulosin
Tamsulosin hydrochloride is absorbed from the intestine and is almost completely available. 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). The steady-state serum concentration (Css) of approx. 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 (approx. 0.2l/kg). Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-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. In vitro results 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 Dutasteride/ Tamsulosin Hydrochloride 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 approx. 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 ($30 \leq CLcr < 70$ mL/min/1.73m^2) or moderate to severe ($10 \leq CLcr < 30$ mL/min/1.73m^2) renal impairment compared with subjects with normal renal function. However, patients with terminal renal disease (CLcr < 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).

Indication
Dutamsuvitae is indicated as combination therapy for the treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

Dutamsuvitae reduces the risk of acute urinary retention and the need for surgery in patients with moderate to severe symptoms of BPH.

Recommended dosage
Patients >21 years old (including elderly patients)
The recommended dose of Dutamsuvitae is one capsule daily (0.5 mg / 0.4 mg).

Dutamsuvitae 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. Dutamsuvitae 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. Dutamsuvitae should be used with caution in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of Dutamsuvitae is contraindicated.

Patients ≤21 years old:
Dutamsuvitae is not indicated in patients ≤21 years old.

Route of administration
Oral

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.

Warning and precautions
Prior to initiating treatment with Dutamsuvitae the patient should be examined to rule out other causes of the symptoms.

Dutamsuvitae 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 Dutamsuvitae 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 Dutamsuvitae 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 Dutamsuvitae 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 Dutamsuvitae do not rule out prostate cancer.

For this reason, after six months of treatment with Dutamsuvitae, 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 Dutamsuvitae 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 Dutamsuvitae. 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 Dutamsuvitae.

Prostate cancer (in particular high grade tumours)
Results of two long-term clinical studies (REDUCE dutasteride study and PCPT finasteride study) in men at increased risk of prostate cancer revealed a higher incidence of Gleason 8 – 10 prostate cancers in men treated 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 Dutamsuvitae should be regularly evaluated for the manifestation of prostate cancer, including PSA testing.

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. In two-year clinical trials with single-agent dutasteride therapy, in which exposure to dutasteride totaling 3,374 patient-years was achieved, and in the two-year open-label extension phase, two cases of breast cancer were reported in patients treated with dutasteride and one case in the placebo group up to the time of registration. In the 4-year CombAT 4 and REDUCE studies there were no cases of breast cancer reported in any treatment groups. Integration of these 2 studies results in exposure of 17,489 patient-years to dutasteride monotherapy and 5,027 patient-years to the combination of dutasteride and tamsulosin.

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. Dutamsuvitae 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 Dutamsuvitae 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
In two studies, both of which were over a four years period, 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
In a fertility study with dutasteride in 50 volunteers there was a reduction in total sperm count, total sperm volume and sperm motility although mean values remained within the normal range. Sperm concentration and morphology were normal. There were major fluctuations in the individual results. In two volunteers there was a 90% reduction in sperm count after 52 weeks, which had partially recovered by the follow- up 24 weeks later. 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, Dutamsuvitae should be used with caution in patients with mild to moderate hepatic impairment. Since also for tamsulosin there are no data regarding severe hepatic impairment available, Dutamsuvitae 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, Dutamsuvitae should basically not be co- administered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, voriconazole, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir).

Dutamsuvitae 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. Dutamsuvitae 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:
Dutamsuvitae 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 Dutamsuvitae:
On discontinuing Dutamsuvitae 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.

Interactions
There have been no drug interaction studies for Dutamsuvitae. 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, and in animal studies in rats and dogs, it did not cause any induction of 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 Cmax 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 Cmax 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 subjects. 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 Dutamsuvitae.

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 Cmax and AUC of tamsulosin hydrochloride; however these changes are clinically irrelevant and no dose adjustment is necessary.

In clinical studies, tamsulosin had no effect on the pharmacokinetics of atenolol, digoxin, enalapril, nifedipine or theophylline.

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

Pregnancy, Lactation and Fertility
Dutamsuvitae is contraindicated in women.

No studies have been conducted with Dutamsuvitae 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.

Lactation:
It is not known whether dutasteride or tamsulosin 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 possibility of reduced male fertility cannot be excluded.

Effects of Tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Adverse effects/Undesirable effects
The most common undesirable effects during combined administration of dutasteride and tamsulosin 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 modo

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

Overdose and treatment
No data are available with regard to overdosage with Dutamsuvitae. 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.

Effects on ability to drive vehicles and use machines
The effect of Dutamsuvitae 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 Dutamsuvitae that could impair the ability to drive and to use machines.

Storage conditions
Store below 30°C, in the sealed original pack.

Dosage forms and packaging available
Dutamsuvitae (Dutasteride/Tamsulosin Hydrochloride 0.5mg/0.4mg hard capsules is packaged in Alu/Alu blister and is availabe in 30 hard capsules Tablet packs.

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MOCK UP Galenicum

Galenicum believe in life