Front

MAXFLOW-S™

(Tamsulosin HCl+Solifenacin Succinate)

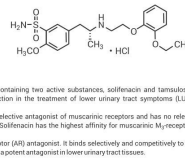
0.4 mg/6 mg Tablet

میکس فلو-ایس

Each tablet contains a layer of 6 mg solifenacin succinate, corresponding to 4.5 mg solifenacin free base and a layer of 0.4 mg tamsulosin hydrochloride, corresponding to 0.37 mg of tamsulosin free base.

COMPOSITION:
Each bi-layered tablet contains:
Tamsulosin HCl (Modified Release) ..... 0.4 mg.
Solifenacin Succinate (Immediate Release) ..... 6 mg.

Product Specs.: Innovator



Mechanism of Action:
A fixed dose combination tablet containing two active substances, solifenacin and tamsulosin. These drugs have independent and complementary mechanisms of action in the treatment of lower urinary tract symptoms (LUTS) associated with BPH, with storage symptoms.
Solifenacin: is a competitive and selective antagonist of muscarinic receptors and has no relevant affinity for various other receptors, enzymes and ion channels tested. Solifenacin has the highest affinity for muscarinic M_3-receptors, followed by muscarinic M_1- and M_2-receptors.
Tamsulosin: is an alpha1-adrenoceptor (AR) antagonist. It binds selectively and competitively to postsynaptic $alpha_{1}$-ARs, in particular to subtypes $alpha_{1A}$ and $alpha_{1D}$ and is a potent antagonist in lower urinary tract tissues.

CLINICAL PHARMACOLOGY:
Pharmacokinetics:
Solifenacin / Tamsulosin:
The information below presents the pharmacokinetic parameters after multiple dosing of Solifenacin / Tamsulosin. A multiple dose relative bioavailability study demonstrated that the administration of Solifenacin / Tamsulosin results in comparable exposure to that of the co-administration of the separate tablets of solifenacin and tamsulosin OCAS of the same dose.
Absorption: After multiple dosing of Solifenacin / Tamsulosin, the t_{max} of solifenacin varied between 4.27 hours and 4.76 hours in different studies; the t_{max} of tamsulosin varied between 3.47 hours and 5.65 hours. The corresponding C_{max} values of solifenacin varied between 26.5 ng/mL and 32.0 ng/mL, while the C_{max} of tamsulosin varied between 6.56 ng/mL and 13.3 ng/mL. The AUC values of solifenacin varied between 528 ng.h/mL and 601 ng.h/mL, and of tamsulosin between 97.1 ng.h/mL and 222 ng.h/mL. The absolute bioavailability of solifenacin is approximately 90%, while for tamsulosin 70 % to 79 % is estimated to be absorbed.
A single dose food effect study was performed with Solifenacin / Tamsulosin dosed under fasted conditions, after a low fat, low caloric breakfast and after a high fat, high caloric breakfast. After a high fat, high caloric breakfast, a 54% increase in C_{max} for the tamsulosin component of Solifenacin / Tamsulosin was observed compared to the fasted state while the AUC increased by 33%. A low fat, low caloric breakfast did not affect the pharmacokinetics of tamsulosin. The pharmacokinetics of the solifenacin component were not affected by either a low fat, low caloric, or a high fat, high caloric breakfast.
Concomitant administration of solifenacin and tamsulosin OCAS resulted in a 1.19-fold increase in the C_{max} and 1.24-fold increase in the AUC of tamsulosin as compared to the AUC of tamsulosin OCAS tablets administered alone. There was no indication of an effect of tamsulosin on the pharmacokinetics of solifenacin.
Elimination: After a single administration of Solifenacin / Tamsulosin, the 1% of solifenacin ranged from 49.5 hours to 53.0 hours and of tamsulosin from 12.8 hours to 14.0 hours.
Multiple doses of verapamil 240 mg q.d. co-administered with Solifenacin / Tamsulosin resulted in a 60% increase in C_{max} and a 63% increase in AUC for solifenacin, while for tamsulosin C_{max} increased by 11.5% and AUC by 122%. The changes in C_{max} and AUC are not considered clinically relevant. Population pharmacokinetic analysis of the phase 3 data showed that intra-subject variability in tamsulosin pharmacokinetics was related to differences in age, height and α_1-acid glycoprotein plasma concentrations. An increase in age and α_1-acid glycoprotein was associated with an increase in AUC, while an increase in height was associated with a decrease in AUC. The same factors resulted in similar changes in the pharmacokinetics of solifenacin. In addition, increases in gamma glutamyl transpeptidase were associated with higher AUC values. These changes in AUC are not considered clinically relevant. Information from the individual active substances used as single entity products complete the pharmacokinetic properties of Solifenacin / Tamsulosin:
Solifenacin:
Absorption: For solifenacin tablets, t_{max} is independent of the dose and occurs 3 to 8 hours after multiple dosing. The C_{max} and AUC increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%.
Distribution: The apparent volume of distribution of solifenacin following intravenous administration is approximately 600 L. Approximately 98% of solifenacin is bound to plasma proteins, primarily α_1-acid glycoprotein.
Biotransformation: Solifenacin has a low first pass effect, being metabolised slowly. Solifenacin is extensively metabolised by the liver, primarily by CYP3A4. However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin is about 9.5 L/h. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxyl-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.
Elimination: After a single administration of 10 mg [14$_C$-labelled] solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).
Tamsulosin:
Absorption: For tamsulosin OCAS, t_{max} occurs 4 to 6 hours after multiple dosing of 0.4 mg/day. C_{max} and AUC increase in proportion to the dose between 0.4 and 1.2 mg. The absolute bioavailability is estimated to be approximately 57%.
Distribution: The volume of distribution of tamsulosin following intravenous administration is about 16 L. Approximately 99% of tamsulosin is bound to plasma proteins, primarily α_1-acid glycoprotein.
Biotransformation: Tamsulosin has a low first pass effect, being metabolised slowly. Tamsulosin is extensively metabolised by the liver, primarily by CYP3A4 and CYP2D6. The systemic clearance of tamsulosin is about 2.9 L/h. Most tamsulosin is present in plasma in the form of unchanged active substance.
None of the metabolites were more active than the original compound.
Elimination: After a single dose of 0.2 mg [14$_C$-labelled] tamsulosin, after 1 week about 76% of radioactivity is excreted in urine and 21% in faeces. In urine, approximately 9% of the radioactivity is recovered as unchanged tamsulosin; about 16% as the sulphate of o-deethylated tamsulosin, and 8% as o-ethoxybenzoy acetic acid.
Characteristics in specific groups of patients:
Older people:
In the clinical pharmacology and biopharmaceutical studies, the age of the subjects varied between 19 and 79 years. After Solifenacin / Tamsulosin administration, the highest mean exposure values were found in elderly subjects, although there was an almost complete overlap with individual values found in younger subjects. This was confirmed by population pharmacokinetic analysis of phase 2 and 3 data. Solifenacin / Tamsulosin can be used in elderly patients.
Renal impairment:
Solifenacin / Tamsulosin: Solifenacin / Tamsulosin can be used in patients with mild to moderate renal impairment, but should be used with caution in patients with severe renal impairment.
The pharmacokinetics of Solifenacin / Tamsulosin have not been studied in patients with renal impairment.
The following statements reflect the information available on the individual components regarding renal impairment.
Solifenacin: The AUC and C_{max} of solifenacin in patients with mild or moderate renal impairment were not significantly different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance < 30 mL/min), exposure to solifenacin was significantly greater than in the controls, with increases in C_{max} of about 30%, AUC of more than 100% and t½ of more than 60%. A statistically significant relationship was observed between creatinine clearance and solifenacin clearance.
Pharmacokinetics in patients undergoing haemodialysis have not been studied.
Patients with end stage renal disease (CrCl < 10 mL/min/1.73 m^2) have not been studied.
Hepatic impairment:
Solifenacin / Tamsulosin:
Solifenacin / Tamsulosin can be used in patients with mild to moderate hepatic impairment, but is contraindicated in patients with severe hepatic impairment.
The pharmacokinetics of Solifenacin / Tamsulosin have not been studied in patients with hepatic impairment. The following statements reflect the information available on the individual components regarding hepatic impairment.
Solifenacin:
In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} was not affected, AUC increased by 60% and t½ doubled. The pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.
Tamsulosin:
The pharmacokinetics of tamsulosin have been compared in 8 subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9) and 8 healthy subjects. While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to α_1-acid glycoprotein, the unbound (active) concentration of tamsulosin did not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin. Tamsulosin has not been studied in patients with severe hepatic impairment.
Pharmacodynamics:
Solifenacin / Tamsulosin tablets consist of two active substances with independent and complementary effects in LUTS associated with BPH, with storage symptoms: Solifenacin antagonizes storage function problems related to non-neurionally released acetylcholine activating M_3-receptors in the bladder. Non-neurionally released acetylcholine sensitizes urothelial sensory function and manifests as urinary urgency and frequency. Tamsulosin improves voiding symptoms (increases the maximum urinary flow rate), by relieving obstruction via relaxation of smooth muscle in prostatic bladder neck and urethra. It also improves storage symptoms.
Clinical efficacy and safety: Efficacy was demonstrated in a pivotal phase 3 study in patients with LUTS associated with BPH with voiding (obstructive) symptoms and at least the following level of storage (irritative) symptoms: ≥ 8 micturitions/24 hours and ≥ 2 urgency episodes/24 hours. Solifenacin / Tamsulosin showed statistically significant improvements from baseline to end of study compared with placebo in the two primary endpoints, total International Prostate Symptom Score (IPSS) and Total Urgency and Frequency Score, and on the secondary endpoints urgency, micturition frequency, mean voided volume per micturition, nocturia, IPSS voiding sub-score, IPSS storage sub-score, IPSS quality of life (QoL), Overactive Bladder questionnaire (OAB-q) Bother score and OAB-q Health Related Quality of Life (HRQoL) score including all sub-scores (coping, concern, sleep and social).
Solifenacin / Tamsulosin showed superior improvement compared with tamsulosin OCAS on Total Urgency and Frequency Score, as well as on micturition frequency, mean voided volume per micturition and IPSS storage sub-score. This was accompanied by significant improvements in IPSS QoL and OAB-Q HRQoL total score including all sub-scores. Furthermore, Solifenacin / Tamsulosin was non-inferior to tamsulosin OCAS on total IPSS (p.<0.001), as expected.

INDICATIONS:
Treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men who are not adequately responding to treatment with monotherapy.

DOSAGE AND ADMINISTRATION:
Adult males, including older people: One Solifenacin / Tamsulosin tablet (6 mg/0.4 mg) once daily taken orally with or without food. The maximum daily dose is one Solifenacin / Tamsulosin tablet (6 mg/0.4 mg). The tablet must be swallowed whole, intact without biting or chewing. Do not crush the tablet.
Patients with renal impairment: The effect of renal impairment on the pharmacokinetics of Solifenacin / Tamsulosin has not been studied. However, the effect on the pharmacokinetics of the individual active substances is well known. Solifenacin / Tamsulosin can be used in patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min). Patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) should be treated with caution and the maximum daily dose in these patients is one Solifenacin / Tamsulosin tablet (6 mg/0.4 mg).
Patients with hepatic impairment: The effect of hepatic impairment on the pharmacokinetics of Solifenacin / Tamsulosin has not been studied. However, the effect on the pharmacokinetics of the individual active substances is well known. Solifenacin / Tamsulosin can be used in patients with mild hepatic impairment (Child-Pugh score <= 7).
Patients with moderate hepatic impairment: (Child-Pugh score 7-9) should be treated with caution and the maximum daily dose in these patients is one Solifenacin / Tamsulosin tablet (6 mg/0.4 mg). In patients with severe hepatic impairment (Child-Pugh score > 9), the use of Solifenacin / Tamsulosin is contraindicated.
Moderate and strong inhibitors of cytochrome P450 3A4: The maximum daily dose of Solifenacin / Tamsulosin should be limited to one tablet (6 mg/0.4 mg). Solifenacin / Tamsulosin should be used with caution in patients treated simultaneously with moderate or strong CYP3A4 inhibitors, e.g. verapamil, ketoconazole, ritonavir, nelfinavir, itraconazole.
Paediatric population: There is no relevant indication for use of Solifenacin / Tamsulosin in children and adolescents.

WARNINGS & PRECAUTIONS:
Solifenacin / Tamsulosin should be used with caution in patients with:
- severe renal impairment,
- risk of urinary retention,
- gastrointestinal obstructive disorders,
- risk of decreased gastrointestinal motility,
- hiatus hernia/gastroesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis,
- autonomic neuropathy.

The patient should be examined in order to exclude the presence of other conditions, which can cause similar symptoms to benign prostatic hyperplasia.
Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Solifenacin / Tamsulosin is initiated. If a urinary tract infection is present, appropriate antibacterial therapy should be started.
QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia, who are treated with solifenacin succinate.
Angioedema with airway obstruction has been reported in some patients on solifenacin succinate and tamsulosin. If angioedema occurs, Solifenacin / Tamsulosin should be discontinued and not be restarted. Appropriate therapy and/or measures should be taken.
Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, Solifenacin / Tamsulosin should be discontinued and appropriate therapy and/or measures should be taken.
As with other $alpha_1$-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients starting treatment with Solifenacin / Tamsulosin should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have disappeared.
The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Therefore, the initiation of therapy with Solifenacin / Tamsulosin in patients for whom cataract or glaucoma surgery is scheduled is not recommended. Discontinuing treatment with Solifenacin / Tamsulosin 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being treated with Solifenacin / Tamsulosin in order to ensure that appropriate measures will be in place to manage IFIS during surgery.
Solifenacin / Tamsulosin should be used with caution in combination with moderate and strong inhibitors of CYP3A4 and it should not be used in combination with strong inhibitors of CYP3A4, e.g., ketoconazole, in patients who are of the CYP2D6 poor metaboliser phenotype or who are using strong inhibitors of CYP2D6, e.g., paroxetine.

ADVERSE REACTIONS:

System Organ Class (SOC) /Preferred Term (PT)	ADR frequency observed with the individual substances	
	Solifenacin 5 mg and 10 mg	Tamsulosin 0.4 mg
Infections and infestations		
Urinary tract infection	Uncommon	
Cystitis	Uncommon	
Immune system disorders		
Anaphylactic reaction	Not known	
Metabolism and nutrition disorders		
Decreased appetite	Not known	
Hyperkalaemia	Not known	
Psychiatric disorders		
Hallucination	Very rare	
Confusional state	Very rare	
Delirium	Not known	
Nervous system disorders		
Dizziness	Rare	Common
Somnolence	Uncommon	

Back

Dysgeusia	Uncommon	
Headache	Rare	Uncommon
Syncope		Rare
Eye disorders		
Vision blurred	Common	Not known
Intraoperative Floppy Iris Syndrome (IFIS)		Not known
Dry eyes	Uncommon	
Glaucoma	Not known	
Visual impairment		Not known
Cardiac disorders		
Palpitations	Not known	Uncommon
Torsade de Pointes	Not known	
Electrocardiogram QT prolongation	Not known	
Atrial fibrillation	Not known	Not known
Arrhythmia		Not known
Tachycardia	Not known	Not known
Vascular disorders		
Orthostatic hypotension		Uncommon
Respiratory, thoracic and mediastinal disorders		
Rhinitis		Uncommon
Nasal dryness	Uncommon	
Dyspnoea		Not known
Dysphonia	Not known	
Epistaxis		Not known
Gastrointestinal disorders		
Dry mouth	Very common	
Dyspepsia	Common	
Constipation	Common	Uncommon
Nausea	Common	Uncommon
Abdominal pain	Common	
Gastro-oesophageal reflux disease	Uncommon	
Diarrhea		Uncommon
Dry throat	Uncommon	
Vomiting	Rare	Uncommon
Colonic obstruction	Rare	
Faecal impaction	Rare	
Ileus	Not known	
Abdominal discomfort	Not known	
Hepatobiliary disorders		
Liver disorder	Not known	
Liver function test abnormal	Not known	
Skin and subcutaneous tissue disorders		
Pruritus	Rare	Uncommon
Dry skin	Uncommon	
Rash	Rare	Uncommon
Urticaria	Very rare	Uncommon
Angioedema	Very rare	Rare
Stevens-Johnson syndrome		Very rare
Erythema multiforme	Very rare	Not known
Exfoliative dermatitis	Not known	Not known
Musculoskeletal and connective tissue disorders		
Muscular weakness	Not known	
Renal and urinary disorders		
Urinary retention***	Rare	
Difficulty in micturition	Uncommon	
Renal impairment	Not known	
Reproductive system and breast disorders		
Ejaculation disorders including retrograde ejaculation and ejaculation failure		Common
Priapism	Very rare	
General disorders and administration site conditions		
Fatigue	Uncommon	
Peripheral oedema	Uncommon	
Asthenia		Uncommon

SPECIAL POPULATIONS:
Older people: In the clinical pharmacology and biopharmaceutical studies, the age of the subjects varied between 19 and 79 years. After Solifenacin / Tamsulosin administration, the highest mean exposure values were found in elderly subjects, although there was an almost complete overlap with individual values found in younger subjects.
Renal impairment:
Solifenacin / Tamsulosin: Solifenacin / Tamsulosin can be used in patients with mild to moderate renal impairment, but should be used with caution in patients with severe renal impairment.
The pharmacokinetics of Solifenacin / Tamsulosin have not been studied in patients with renal impairment.
The following statements reflect the information available on the individual components regarding renal impairment.
Solifenacin: The AUC and C_{max} of solifenacin in patients with mild or moderate renal impairment were not significantly different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance < 30 mL/min), exposure to solifenacin was significantly greater than in the controls, with increases in C_{max} of about 30%, AUC of more than 100% and t½ of more than 60%. A statistically significant relationship was observed between creatinine clearance and solifenacin clearance.
Pharmacokinetics in patients undergoing haemodialysis have not been studied.
Tamsulosin: The pharmacokinetics of tamsulosin have been compared in 6 subjects with mild to moderate (30 < CrCl < 70 mL/min/1.73 m^2) or severe (< 30 mL/min/1.73 m^2) renal impairment and 6 healthy subjects (CrCl > 90 mL/min/1.73 m^2). While a change in the overall plasma concentration of tamsulosin was observed as the result of altered binding to α_1-acid glycoprotein, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Patients with end stage renal disease (CrCl < 10 mL/min/1.73 m^2) have not been studied.
Hepatic impairment:
Solifenacin / Tamsulosin:
Solifenacin / Tamsulosin can be used in patients with mild to moderate hepatic impairment, but is contraindicated in patients with severe hepatic impairment.
The pharmacokinetics of Solifenacin / Tamsulosin have not been studied in patients with hepatic impairment.

Fertility: The effect of Solifenacin / Tamsulosin on fertility has not been established. Animal studies with solifenacin or tamsulosin do not indicate harmful effects on fertility and early embryonic development.
Ejaculation disorders have been observed in short and long term clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported in the post authorization phase.

PREGNANCY AND LACTATION: Solifenacin / Tamsulosin is not indicated for use in women.

CONTRAINDICATIONS:
- Patients with hypersensitivity to the active substance(s) or to any of the excipients
- Patients undergoing haemodialysis
- Patients with severe hepatic impairment
- Patients with severe renal impairment who are also treated with a strong cytochrome P450 (CYP) 3A4 inhibitor, e.g., ketoconazole
- Patients with moderate hepatic impairment who are also treated with a strong CYP3A4 inhibitor, e.g., ketoconazole
- Patients with severe gastrointestinal conditions (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and patients at risk for these conditions.
- Patients with a history of orthostatic hypotension.

DRUG INTERACTIONS:
Concomitant medication with any medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with Solifenacin / Tamsulosin, before commencing any anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.
Interactions with CYP3A4 and CYP2D6 inhibitors:
Concomitant administration of solifenacin with ketoconazole (a strong inhibitor of CYP3A4) (200 mg/day) resulted in a 1.4- and 2.0-fold increase in C_{max} and area under the curve (AUC) of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a 1.5- and 2.8-fold increase in C_{max} and AUC of solifenacin.
Concomitant administration of tamsulosin with ketoconazole at a dose of 400 mg/day resulted in a 2.2- and 2.8-fold increase in C_{max} and AUC of tamsulosin, respectively.
Since concomitant administration with strong inhibitors of CYP3A4, such as ketoconazole, ritonavir, nelfinavir and itraconazole may lead to increased exposure to both solifenacin and tamsulosin, Solifenacin / Tamsulosin should be used with caution in combination with strong CYP3A4 inhibitors.
Solifenacin / Tamsulosin should not be given together with strong CYP3A4 inhibitors in patients who are also CYP2D6 poor metaboliser phenotype or who are already using strong CYP2D6 inhibitors.
Concomitant administration of Solifenacin / Tamsulosin with verapamil (a moderate CYP3A4 inhibitor) resulted in an approximately 2.2-fold increase in C_{max} and AUC of tamsulosin and an approximately 1.6-fold increase in the C_{max} and AUC of solifenacin. Solifenacin / Tamsulosin should be used with caution in combination with moderate inhibitors of CYP3A4.
Concomitant administration of tamsulosin with the weak CYP3A4 inhibitor cimetidine (400 mg every 6 hours) resulted in a 1.44-fold increase in the AUC of tamsulosin, while C_{max} was not significantly changed. Solifenacin / Tamsulosin can be used with weak CYP3A4 inhibitors.
Concomitant administration of tamsulosin with the strong CYP2D6 inhibitor paroxetine (20 mg/day) resulted in an increase in C_{max} and AUC of tamsulosin by 1.3- and 1.6-fold, respectively. Solifenacin / Tamsulosin can be used with CYP2D6 inhibitors.
The effect of enzyme induction on the pharmacokinetics of solifenacin and tamsulosin has not been studied. Since solifenacin and tamsulosin are metabolised by CYP3A4, pharmacokinetic interactions are possible with CYP3A4 inducers (e.g., rifampicin) which may decrease the plasma concentration of solifenacin and tamsulosin.

OTHER INTERACTIONS:
The following statements reflect the information available on the individual active substances.
Solifenacin:
- Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.
- In vitro studies with solifenacin have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4. Therefore, no interactions are expected between solifenacin and drugs metabolised by these CYP enzymes.
- Intake of solifenacin did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.
- Intake of solifenacin showed no effect on the pharmacokinetics of digoxin.

Tamsulosin:
- Co-administration with other $alpha_1$-adrenoceptor antagonists could lead to hypotensive effects.
- In vitro, the free fraction of tamsulosin in human plasma was not changed by diazepam, propranolol, trichlormethiazide, chlormadinone, amitriptyline, diclofenac, glibenclamide, simvastatin or warfarin. Tamsulosin does not change the free fraction of diazepam, propranolol, trichlormethiazide or chlormadinone. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin.
- Co-administration with furosemide causes a fall in plasma levels of tamsulosin, but as levels remain within the normal range, concurrent use is acceptable.
- In vitro studies with tamsulosin have demonstrated that at therapeutic concentrations, tamsulosin does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. Therefore, no interactions are expected between tamsulosin and drugs metabolised by these CYP enzymes.
- No interactions have been seen when tamsulosin was given concomitantly with atenolol, enalapril, or theophylline.

INSTRUCTIONS:
- Store below 30°C.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
MAXFLOW-S 0.4 mg/6 mg Tablet : Pack of 1 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
Horizon Healthcare (Pvt.) Ltd.
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FOR FURTHER INFORMATIONS PLEASE CONTACT

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