Tamsolin®-S

[Tamsulosin HCl + Solifenacin Succinate]

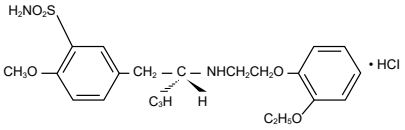
ٹیمسولن-ایس

Tablets 0.4mg + 6mg

DESCRIPTION

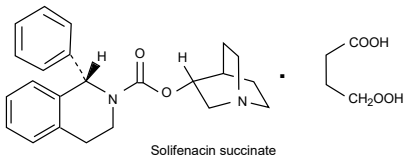
Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) is a fixed dose combination tablet containing two active substances tamsulosin HCl, an antagonist of α_{1a} adrenoceptors in the prostate and solifenacin succinate, a muscarinic receptor antagonist.

Chemically, Tamsulosin HCl is (-)-(R)-5-[2-[[2-(o-Ethoxyphenoxy) ethyl] amino] Propyl]-2- methoxybenzenesulfonamide, monohydrochloride. Its molecular formula is $C_{20}H_{28}N_2O_5S$•HCl and the structural formula is:



Tamsulosin HCl

Chemically, solifenacin succinate is butanedioic acid, compound with (1S)-(3R)-1-azabicyclo [2.2.2] oct-3-yl 3, 4-dihydro-1-phenyl-2(1H) -iso-quinolinecarboxylate (1:1) having molecular formula of $C_{23}H_{26}N_2O_2.C_4H_6O_4$ and the structural formula is:



Solifenacin succinate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet is available for oral administration as:

Tamsolin-S Tablets 0.4mg + 6mg
Each modified release tablet contains:
Tamsulosin HCl USP…….0.4mg
Solifenacin succinate……..6mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Tamsulosin HCl:

Tamsulosin HCl is an α_1-adrenoceptor (AR) antagonist. It binds selectively and competitively to postsynaptic α_1-ARs, in particular to subtypes α_{1a} and α_{1d} and is a potent antagonist in lower urinary tract tissues.

Solifenacin succinate:

Solifenacin succinate is a competitive and selective antagonist of muscarinic receptors and has no relevant affinity for various other receptors, enzymes and ion channels tested. Solifenacin succinate has the highest affinity for muscarinic M_3-receptors, followed by muscarinic M_1- and M_2- receptors.

Pharmacokinetics

The absolute bioavailability of solifenacin succinate is approximately 90%, while for tamsulosin HCl 70% to 79% is estimated to be absorbed. A low fat, low caloric breakfast did not affect the pharmacokinetics of tamsulosin HCl. After a high fat, high caloric breakfast, a 54% increase in C_{max} for the tamsulosin HCl, was observed compared to the fasted state while the AUC increased by 33%. The pharmacokinetics of the solifenacin succinate component was not affected by either a low fat, low caloric or a high fat, high caloric breakfast.

Concomitant administration of tamsulosin HCl and solifenacin succinate resulted in a 1.24-fold increase in the AUC of tamsulosin HCl and 1.19-fold increase in the C_{max} as compared to the AUC of tamsulosin HCl tablets administered alone.

Absorption

Tamsulosin HCl

For tamsulosin HCl, t_{max} occurs 4 to 6 hours after multiple dosing of 0.4mg/day. C_{max} and AUC increase in proportion to the dose between 0.4mg and 1.2mg. The absolute bioavailability is estimated to be approximately 57%.

Solifenacin succinate

For Solifenacin succinate 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 5mg to 40mg. Absolute bioavailability is approximately 90%.

Distribution

Tamsulosin HCl

The volume of distribution of tamsulosin HCl following intravenous administration is about 16 L. Approximately 99% of tamsulosin HCl is bound to plasma proteins, primarily α_1-acid glycoprotein.

Solifenacin succinate

The apparent volume of distribution of solifenacin succinate following intravenous administration is approximately 600 L. Approximately 98% of solifenacin succinate is bound to plasma proteins, primarily α_1-acid glycoprotein.

Metabolism

Tamsulosin HCl

Tamsulosin HCl has a low first pass effect, being metabolised slowly. Tamsulosin HCl is extensively metabolised by the liver, primarily by CYP3A4 and CYP2D6. The systemic clearance of tamsulosin HCl is about 2.9 L/h. Most tamsulosin HCl is present in plasma in the form of unchanged active substance. None of the metabolites were more active than the original compound.

Solifenacin succinate

Solifenacin succinate has a low first pass effect, being metabolised slowly. Solifenacin succinate is extensively metabolised by the liver, primarily by CYP3A4. However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin succinate. The systemic clearance of solifenacin succinate 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 succinate.

Elimination

After single administration of Tamsulosin HCl + Solifenacin succinate, $t_{1/2}$ of tamsulosin HCl ranged from 12.8 hours to 14.0 hours and of solifenacin ranged from 49.5 hours to 53 hours.

Tamsulosin HCl

After a single dose of 0.2mg [^{14}C-labelled]-tamsulosin HCl, after 1 week about 76% of radioactivity is excreted in urine and 21% in feces. In urine, approximately 9% of the radioactivity is recovered as unchanged tamsulosin HCl; about 16% as the sulphate of o-deethylated tamsulosin HCl and 8% as o-ethoxyphenoxy acetic acid.

Solifenacin succinate

After a single administration of 10mg [^{14}C-labelled]-solifenacin, about 70% of the radioactivity was detected in urine and 23% in feces 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).

THERAPEUTIC INDICATIONS

Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) is indicated for the 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 Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg once daily taken orally with or without food. The maximum daily dose is one Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg.

Special Population

Patients with renal impairment

Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) can be used in patients with mild to moderate renal impairment (CrCL > 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 Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg.

Patients with hepatic impairment

Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg 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 Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg. In patients with severe hepatic impairment (Child-Pugh score > 9), the use of Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg is contraindicated.

Moderate and strong inhibitors of cytochrome P450 3A4

The maximum daily dose of Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg should be limited to one tablet. Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablet 0.4mg + 6mg should be used with caution in patients treated simultaneously with moderate or strong CYP3A4 inhibitors, e.g. verapamil, ketoconazole, ritonavir, nelfinavir, itraconazole.

CONTRAINDICATIONS

Tamsulosin HCl + Solifenacin succinate is contraindicated in:

- Patients with hypersensitivity to the active substance(s) or to any of the excipient of the product.
- Patients undergoing hemodialysis.
- 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.

- Combination of tamsulosin HCl + solifenacin succinate is not indicated for use in:
  - Women
  - Children
  - Adolescent

PRECAUTIONS
- Combination of tamsulosin HCl + solifenacin succinate 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/gastro esophageal 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 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 hypokalemia, who are treated with solifenacin succinate.
- Angioedema with airway obstruction has been reported in some patients on tamsulosin HCl + solifenacin succinate. If angioedema occurs, treatment should be discontinued and not 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, treatment should be discontinued and appropriate therapy and/or measures should be taken.
- As with other α_1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin HCl, as a result of which, rarely, syncope can occur. Patients starting treatment with tamsulosin HCl + solifenacin succinate should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have disappeared.
- During pre-operative assessment, surgeons and ophthalmic team should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with tamsulosin HCl + solifenacin succinate in order to ensure that appropriate measure will be in place to manage 'Intraoperative Floppy Iris Syndrome' (IFIS) during surgery.
- Combination of tamsulosin HCl + solifenacin succinate 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 metabolizer phenotype.

ADVERSE REACTIONS
Tamsulosin HCl
Common: Dizziness, ejaculation disorder including retrograde ejaculation and ejaculation failure.
Uncommon: Headache, orthostatic hypotension, rhinitis, constipation, nausea, diarrhea, vomiting, pruritus, rash, urticaria and asthenia.
Rare: Syncope and angioedema.

Solifenacin succinate
Very common: Dry mouth.
Common: Constipation, nausea, dyspepsia, abdominal pain and blurred vision.
Uncommon: Gastro esophageal reflux diseases, dry throat, urinary tract infection, cystitis, somnolence, dysgeusia, dry eyes, fatigue, peripheral edema, nasal dryness, dry skin and difficulty in micturation.
Rare: Colonic obstruction, fecal impaction and urinary retention, dizziness, headache, vomiting, pruritus and rash.

DRUG INTERACTION
- 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 tamsulosin HCl + solifenacin succinate, before commencing any anticholinergic therapy. The therapeutic effect of solifenacin succinate may be reduced by concomitant administration of cholinergic receptor agonists.
- Concomitant administration of solifenacin with ketoconazole (200mg/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 400mg/day resulted in a 1.5- and 2.8-fold increase in C_{max} and AUC of solifenacin.
- Concomitant administration of tamsulosin HCl with ketoconazole at a dose of 400mg/day resulted in a 2.2- and 2.8-fold increase in C_{max} and AUC of tamsulosin HCl, respectively.
- Concomitant administration of tamsulosin HCl + solifenacin succinate with verapamil resulted in an approximately 2.2-fold increase in C_{max} and AUC of tamsulosin HCl and an approximately 1.6-fold increase in the C_{max} and AUC of solifenacin succinate. Tamsulosin HCl + solifenacin succinate should be used with caution in combination with moderate inhibitors of CYP3A4.
- Concomitant administration of tamsulosin HCl with the weak CYP3A4 inhibitor cimetidine (400mg every 6 hours) resulted in a 1.44-fold increase in the AUC of tamsulosin HCl. Tamsulosin HCl + solifenacin succinate can be used with weak CYP3A4 inhibitors.
- Concomitant administration of tamsulosin HCl with the strong CYP2D6 inhibitor paroxetine (20mg/day) resulted in an increase in C_{max} and AUC of tamsulosin HCl by 1.3- and 1.6-fold, respectively. Tamsulosin HCl + solifenacin succinate can be used with CYP2D6 inhibitors.
- Solifenacin succinate can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.
- Co-administration with other α_1-adrenoceptor antagonists could lead to hypotensive effects.
- Pharmacokinetic interactions are possible with CYP3A4 inducers (e.g., rifampicin) which may decrease the plasma concentration of tamsulosin HCl and solifenacin succinate.

OVERDOSAGE
Symptoms
Overdosage with the combination of tamsulosin HCl + solifenacin succinate can potentially result in severe anticholinergic effects plus acute hypotension.

Treatment
In the event of overdose with tamsulosin HCl + solifenacin succinate, the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour, but vomiting should not be induced.
As for other anticholinergics, symptoms of overdose due to the solifenacin succinate component can be treated as follows:
- *Severe central anticholinergic effects such as hallucinations or pronounced excitation:* Treat with physostigmine or carbachol.
- *Convulsions or pronounced excitation:* Treat with benzodiazepines.
- *Respiratory insufficiency:* Treat with artificial respiration.
- *Tachycardia:* Treat symptomatically if needed. β-blockers should be used with caution, since the concomitant overdose with tamsulosin HCl could potentially induce severe hypotension.
- *Urinary retention:* Treat with catheterisation.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with a known risk for QT-prolongation (i.e., hypokalemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e., myocardial ischemia, arrhythmia, congestive heart failure).
Acute hypotension, which can occur after overdosage due to the tamsulosin HCl component, should be treated symptomatically. Hemodialysis is unlikely to be of help as tamsulosin HCl is very highly bound to plasma proteins.

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Tamsolin-S (Tamsulosin HCl + Solifenacin succinate) Tablets 0.4mg + 6mg are available in blister pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
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