

## DUOFLO Combipack (Tamsulosin hydrochloride + Solifenacin succinate)

### Composition

DUOFLO Capsules and Tablets

Each combipack contains:

10 Tamsulosin Hydrochloride Modified-release Capsules 400 mcg &

10 Solifenacin Succinate Tablets 5 mg

A. Tamsulosin Hydrochloride Modified-release Capsules 400 mcg

Each capsule contains:

Tamsulosin Hydrochloride IP ..... 400 mcg

(As modified-release pellets)

Colours used in empty capsule shell- Brilliant Blue, Carmoisine, Sunset yellow and Titanium Dioxide IP.

A. Solifenacin Succinate Tablets 5 mg

Each film-coated tablet contains:

Solifenacin Succinate.....5 mg

Colours: Yellow Oxide of Iron & Titanium Dioxide IP

### Dosage Form/s

Capsule and Tablet

### Description

DUOFLO is available as a combipack containing two active substances, tamsulosin hydrochloride and solifenacin succinate, with independent and complementary effects in lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH), with storage symptoms:

- Solifenacin ameliorates storage function problems related to non-neuronally released acetylcholine activating M<sub>3</sub>-receptors in the bladder. Non-neuronally 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 prostate, bladder neck and urethra. It also improves storage symptoms.

### Pharmacology

#### ▶ Pharmacodynamics

*Tamsulosin Hydrochloride*

*Mechanism of Action*

The symptoms associated with BPH are related to bladder outlet obstruction, which comprises two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck, leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of  $\alpha_1$  adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. Tamsulosin, an  $\alpha_1$ -adrenoceptor blocking agent, exhibits selectivity for  $\alpha_{1A}$ -receptors in the human prostate. At least three discrete  $\alpha_1$ -adrenoceptor subtypes have been identified:  $\alpha_{1A}$ ,  $\alpha_{1B}$ , and  $\alpha_{1D}$ ; their distribution differs between human organs and tissue. Approximately 70% of the  $\alpha_1$ -receptors in the human prostate are of the  $\alpha_{1A}$  subtype. Tamsulosin hydrochloride is not intended for use as an antihypertensive drug.

### ► Pharmacodynamics

Urologic pharmacodynamic effects have been evaluated in neurologically impaired pediatric patients and in adults with BPH

#### *Solifenacin Succinate*

##### Mechanism of Action

Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion.

##### Cardiac Electrophysiology

The effect of 10 mg and 30 mg solifenacin succinate on the QT interval was evaluated at the time of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo- and positive-controlled (moxifloxacin 400 mg) trial. Subjects were randomized to one of two treatment groups after receiving placebo and moxifloxacin sequentially. One group (n=51) went on to complete 3 additional sequential periods of dosing with solifenacin 10, 20 and 30 mg while the second group (n=25), in parallel, completed a sequence of placebo and moxifloxacin. Study subjects were female volunteers aged 19 to 79 years. The 30 mg dose of solifenacin succinate (three times the highest recommended dose) was chosen for use in this study because this dose results in a solifenacin exposure that covers those observed upon co-administration of 10 mg solifenacin succinate with potent cytochrome (CY) P3A4 inhibitors (e.g. ketoconazole 400 mg). Due to the sequential dose-escalating nature of the study, baseline EKG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days.

The median difference from baseline in heart rate associated with the 10 and 30 mg doses of solifenacin succinate compared to placebo was -2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analysed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis. Representative results are shown in Table 1.

Table 1: QTc changes in msec (90%CI) from baseline at Tmax (relative to placebo)\*

Drug/Dose	Fridericia Method (Using Mean Difference)
Solifenacin 10 mg	2 (-3,6)

Solifenacin 30 mg

8 (4,13)

\*Results displayed are those derived from the parallel design portion of the study and represent the comparison of Group 1 to time-matched placebo effects in Group 2.

Moxifloxacin was included as a positive control in this study and, given the length of the study; its effect on the QT interval was evaluated in three different sessions. The placebo-subtracted mean changes (90% CI) in QTcF for moxifloxacin in the three sessions were 11 (7, 14), 12 (8, 17), and 16 (12, 21), respectively.

The QT interval-prolonging effect appeared greater for the 30 mg compared to the 10 mg dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control, moxifloxacin, at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

#### ► Pharmacokinetics

##### *Tamsulosin Hydrochloride*

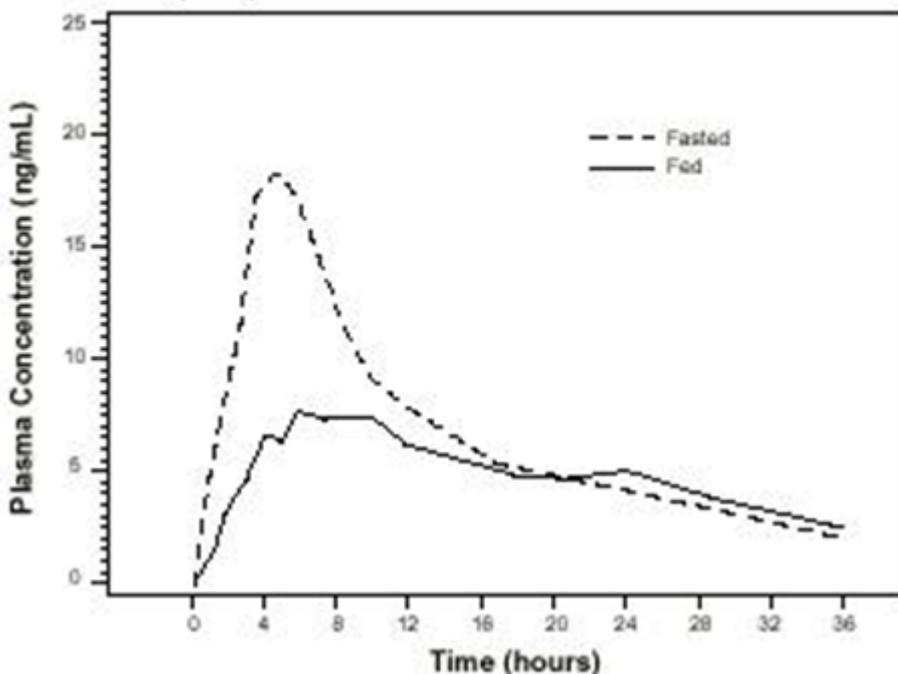
The pharmacokinetics of tamsulosin hydrochloride have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

**Absorption:** Absorption of tamsulosin hydrochloride is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

**Effect of Food:** The time to maximum concentration ( $T_{max}$ ) is reached by 4 to 5 hours under fasting conditions and by 6 to 7 hours when tamsulosin hydrochloride is administered with food.

Taking tamsulosin hydrochloride capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations ( $C_{max}$ ) compared to fed conditions (Figure 1).

Figure 1: Mean plasma tamsulosin hydrochloride concentrations following single-dose administration of tamsulosin hydrochloride 0.4 mg Under Fasted and Fed Conditions (n=8)



The effects of food on the pharmacokinetics of tamsulosin hydrochloride are consistent regardless of whether a tamsulosin capsule is taken with a light breakfast or a high-fat breakfast (Table 2).

Table 2: Mean ( $\pm$  S.D.) pharmacokinetic parameters following tamsulosin capsules 0.4 mg once daily or 0.8 mg once

daily with a light breakfast, high-fat breakfast or fasted

Pharmacokinetic Parameter	0.4 mg QD to healthy volunteers; n=23 (age range 18-32 years)		0.8 mg QD to healthy volunteers; n=22 (age range 55-75 years)			
	Light	Fasted	Light	High-Fat	Fasted	
	Breakfast		Breakfast	Breakfast		
$C_{min}$ (ng/mL)	4.0 ± 2.6	3.8 ± 2.5	12.3 ± 6.7	13.5 ± 7.6	13.3 ± 13.3	
$C_{max}$ (ng/mL)	10.1 ± 4.8	17.1 ± 17.1	29.8 ± 10.3	29.1 ± 11.0	41.6 ± 15.6	
Cmax/Cmin Ratio	3.1 ± 1.0	5.3 ± 2.2	2.7 ± 0.7	2.5 ± 0.8	3.6 ± 1.1	
$T_{max}$ (hours)	6.0	4.0	7.0	6.6	5.0	
$T_{1/2}$ (hours)	-	-	-	-	14.9 ± 3.9	
AUC (ng hr/mL)	151 ± 81.5	199 ± 94.1	440 ± 195	449 ± 217	557 ± 257	

$C_{min}$  = observed minimum concentration

$C_{max}$  = observed maximum tamsulosin hydrochloride plasma concentration

$T_{max}$  = median time-to-maximum concentration

$T_{1/2}$  = observed half-life

AUC = area under the tamsulosin hydrochloride plasma time curve over the dosing interval

**Distribution:** The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to 10 healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94-99%), primarily alpha<sub>1</sub>-acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of tamsulosin hydrochloride to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin hydrochloride had no effect on the extent of binding of these drugs.

**Metabolism:** There is no enantiomeric bioconversion from tamsulosin hydrochloride to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6 as well as via some minor participation of other CYP isoenzymes. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin hydrochloride and amitriptyline, albuterol (beta-agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, results of the *in vitro* testing of the tamsulosin hydrochloride interaction with diclofenac and warfarin were equivocal.

**Excretion:** On administration of the radiolabelled dose of tamsulosin hydrochloride to 4 healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to faeces (21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin hydrochloride in plasma ranged from 5 to 7 hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin hydrochloride, the apparent half-life of tamsulosin hydrochloride is approximately 9–13 hours in healthy volunteers and 14–15 hours in the target population. Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

#### Pharmacokinetics in Special Populations

*Paediatric Use:* Tamsulosin hydrochloride is not indicated for use in paediatric populations.

*Geriatric (Age) Use:* Cross-study comparison of tamsulosin hydrochloride overall exposure (AUC) and half-life indicates that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

*Renal Impairment:* The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ( $30 \leq CL_{cr} < 70$  mL/min/1.73 m<sup>2</sup>) or moderate-severe ( $10 \leq CL_{cr} < 30$  mL/min/1.73 m<sup>2</sup>) renal impairment and 6 normal subjects ( $CL_{cr} > 90$  mL/min/1.73 m<sup>2</sup>). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride dosing. However, patients with end-stage renal disease ( $CL_{cr} < 10$  mL/min/1.73 m<sup>2</sup>) have not been studied.

*Hepatic Impairment:* The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic impairment (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly, with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic impairment do not require an adjustment in tamsulosin hydrochloride capsules dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic impairment.

#### *Solifenacin Succinate*

*Absorption:* After oral administration of solifenacin succinate to healthy volunteers, peak plasma levels ( $C_{max}$ ) of solifenacin are reached within 3–8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg solifenacin succinate tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

*Effect of Food:* Solifenacin succinate may be administered without regard to meals. A single 10 mg dose administration of solifenacin succinate with food increased  $C_{max}$  and AUC by 4% and 3%, respectively.

*Distribution:* Solifenacin succinate is approximately 98% (*in vivo*) bound to human plasma proteins, principally to  $\alpha_1$ -acid glycoprotein. Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600L.

*Metabolism:* Solifenacin succinate is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of the tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically

inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

**Excretion:** Following the administration of 10 mg of <sup>14</sup>C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the faeces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and, in faeces, 4R-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45–68 hours.

#### *Pharmacokinetics in Special Populations*

**Renal Impairment:** Solifenacin succinate should be used with caution in patients with renal impairment. There is a 2.1-fold increase in AUC and 1.6-fold increase in the  $t_{1/2}$  of solifenacin in patients with severe renal impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with severe renal impairment ( $CL_{cr} < 30$  mL/min).

**Hepatic Impairment:** Solifenacin succinate should be used with caution in patients with reduced hepatic function. There is a 2-fold increase in the  $t_{1/2}$  and 35% increase in the AUC of solifenacin in patients with moderate hepatic impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C).

**Gender:** The pharmacokinetics of solifenacin is not significantly influenced by gender.

## Indications

DUOFLO is indicated for the treatment of moderate-to-severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with BPH in men who are not adequately responding to treatment with monotherapy.

## Dosage And Administration

One capsule of tamsulosin hydrochloride (0.4 mg) and one tablet of solifenacin succinate (5 mg) should be taken together with or without food, at the same time once daily. The capsules and tablets should be swallowed whole and should not be crushed or chewed.

#### *Special Populations*

##### *Renal Impairment*

##### *Tamsulosin Hydrochloride*

Patients with renal impairment do not require an adjustment in tamsulosin hydrochloride dosing. However, patients with end-stage renal disease ( $CL_{cr} < 10$  mL/min/1.73 m<sup>2</sup>) have not been studied.

##### *Solifenacin Succinate*

For patients with severe renal impairment ( $CL_{cr} < 30$  mL/min), a daily dose of solifenacin succinate greater than 5 mg is not recommended.

##### *Hepatic Impairment*

##### *Tamsulosin Hydrochloride*

Patients with moderate hepatic impairment do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic impairment.

##### *Solifenacin Succinate*

For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of solifenacin succinate greater than 5 mg is not recommended. Use of solifenacin succinate in patients with severe hepatic impairment

(Child-Pugh C) is not recommended.

## Contraindications

Tamsulosin hydrochloride is contraindicated in patients known to be hypersensitive to tamsulosin hydrochloride or any component of the formulation. Reactions have included skin rash, urticaria, pruritus, angioedema, and respiratory symptoms.

Solifenacin succinate is contraindicated in patients with:

- urinary retention;
- gastric retention;
- uncontrolled narrow-angle glaucoma; and
- in patients who have demonstrated hypersensitivity to the drug.

## Warnings And Precautions

### ► General

#### *Tamsulosin Hydrochloride*

##### Orthostasis

The signs and symptoms of orthostasis (postural hypotension, dizziness, and vertigo) were detected more frequently in tamsulosin hydrochloride treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents, there is a potential risk of syncope. Patients beginning treatment with tamsulosin hydrochloride should be cautioned to avoid situations in which injury could result should syncope occur.

##### Priapism

Rarely (probably less than 1 in 50,000 patients), tamsulosin, like other alpha<sub>1</sub>-antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition.

##### Screening for Prostate Cancer

Prostate cancer and BPH frequently co-exist; therefore, patients should be screened for the presence of prostate cancer prior to treatment with tamsulosin hydrochloride and at regular intervals afterwards.

##### Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in some patients on or previously treated with alpha<sub>1</sub> blockers, including tamsulosin hydrochloride.

Most reports were in patients taking the alpha<sub>1</sub>-blocker when IFIS occurred, but in some cases, the alpha<sub>1</sub>-blocker had been stopped prior to surgery. In most of these cases, the alpha<sub>1</sub>-blocker had been stopped recently prior to surgery (2-14 days), but in a few cases, IFIS was reported after the patient had been off the alpha<sub>1</sub>-blocker for a longer period (5 weeks-9 months). IFIS is a variant of small pupil syndrome and is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings or viscoelastic substances.

IFIS may increase the risk of eye complications during and after the operation. The benefit of stopping alpha<sub>1</sub>-blocker therapy prior to cataract or glaucoma surgery has not been established. The initiation of

therapy with tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended.

#### Sulpha Allergy

In patients with sulpha allergy, allergic reaction to tamsulosin hydrochloride has been rarely reported. If a patient reports a serious or life-threatening sulpha allergy, caution is warranted when administering tamsulosin hydrochloride.

#### Solifenacin Succinate

##### Angioedema and Anaphylactic Reactions

Angio-oedema of the face, lips, tongue and/or larynx have been reported with solifenacin. In some cases, angio-oedema occurred after the first dose. Cases of angio-oedema have been reported to occur hours after the first dose or after multiple doses. Angio-oedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx or larynx occurs, solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided. Anaphylactic reactions have been reported rarely in patients treated with solifenacin succinate. Solifenacin succinate should not be used in patients with a known or suspected hypersensitivity to solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

##### Urinary Retention

Solifenacin, like other anticholinergic drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

##### Gastrointestinal Disorders

Solifenacin like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

##### Central Nervous System Effects

Solifenacin is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including headache, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how solifenacin succinate affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

##### Controlled Narrow-Angle Glaucoma

Solifenacin should be used with caution in patients being treated for narrow-angle glaucoma.

##### Patients with Congenital or Acquired QT Prolongation

In a study of the effect of solifenacin on the QT interval in 76 healthy women, the QT-prolonging effect appeared less with solifenacin 10 mg than with 30 mg (three times the maximum recommended dose), and the effect of solifenacin 30 mg did not appear as large as that of the positive control, moxifloxacin, at its therapeutic dose. This observation should be considered in clinical decisions to prescribe solifenacin succinate for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

#### ▶ Drug Interactions

##### Tamsulosin Hydrochloride

##### Cytochrome P450 Inhibition

##### Strong and Moderate Inhibitors of CYP3A4 or CYP2D6

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) resulted in an increase in the  $C_{max}$

and AUC of tamsulosin by a factor of 2.2 and 2.8, respectively. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g. erythromycin) on the pharmacokinetics of tamsulosin hydrochloride have not been evaluated.

Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in an increase in the  $C_{max}$  and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively. A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin hydrochloride 0.4 mg is co-administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin hydrochloride 0.4 mg should not be used in combination with strong inhibitors of CYP3A4 (e.g. ketoconazole).

The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g. terbinafine) on the pharmacokinetics of tamsulosin hydrochloride have not been evaluated.

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin hydrochloride have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin hydrochloride 0.4 mg is co-administered with a combination of both CYP3A4 and CYP2D6 inhibitors.

#### *Cimetidine*

Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin hydrochloride, which resulted in a moderate increase in tamsulosin hydrochloride AUC (44%).

#### *Other Alpha-Adrenergic Blocking Agents*

The pharmacokinetic and pharmacodynamic interactions between tamsulosin hydrochloride and other alpha-adrenergic blocking agents have not been determined; however, interactions between tamsulosin hydrochloride and other alpha-adrenergic blocking agents may be expected.

#### *PDE5 Inhibitors*

Caution is advised when alpha-adrenergic blocking agents, including tamsulosin hydrochloride, are co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

#### *Warfarin*

A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

#### *Nifedipine, Atenolol, Enalapril*

Dosage adjustments are not necessary when tamsulosin hydrochloride is administered concomitantly with nifedipine, atenolol, or enalapril.

#### *Digoxin and Theophylline*

Dosage adjustments are not necessary when a tamsulosin hydrochloride is administered concomitantly with digoxin or theophylline.

#### *Furosemide*

Tamsulosin hydrochloride had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin hydrochloride  $C_{max}$  and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride dosage.

#### *Solifenacin Succinate*

#### *Potent CYP3A4 Inhibitors*

Following the administration of 10 mg of solifenacin succinate in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean  $C_{max}$  and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5 mg daily dose of solifenacin succinate when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. The effects of weak or moderate CYP3A4 inhibitors were not examined.

#### *CYP3A4 Inducers*

There were no *in vivo* studies conducted to evaluate the effect of CYP3A4 inducers on solifenacin succinate. *In vitro* drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Therefore, inducers of CYP3A4 may decrease the concentration of solifenacin.

#### *Drugs Metabolized by CYP450*

At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

#### *Warfarin*

Solifenacin has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin.

#### *Oral Contraceptives*

In the presence of solifenacin, there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl oestradiol/levonorgestrel).

#### *Digoxin*

Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.

### ▶ Information for Patients

#### *Tamsulosin Hydrochloride*

##### *Hypotension*

Advise the patient about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when taking tamsulosin hydrochloride, and they should be cautioned about driving, operating machinery, or performing hazardous tasks.

##### *Drug Interactions*

Advise the patients that tamsulosin hydrochloride should not be used in combination with strong inhibitors of CYP3A4.

##### *Priapism*

Advise the patient that about the possibility of priapism as a result of treatment with tamsulosin hydrochloride and other similar medications. Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

##### *Screening for Prostate Cancer*

Prostate cancer and BPH frequently co-exist; therefore, screen patients for the presence of prostate cancer prior to treatment with tamsulosin hydrochloride and at regular intervals afterwards.

##### *Intraoperative Floppy Iris Syndrome*

Advise patients when considering cataract or glaucoma surgery to tell their ophthalmologist that they have taken tamsulosin hydrochloride capsules.

##### *Administration*

Patients should be advised not to crush, chew or open tamsulosin hydrochloride capsules.

##### *Solifenacin Succinate*

Patients should be informed that antimuscarinic agents such as solifenacin succinate have been associated with constipation and blurred vision. Patients should be advised to contact their physician if they experience

severe abdominal pain or become constipated for 3 or more days. Because solifenacin succinate may cause blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effect on the patient's vision has been determined. Heat prostration (due to decreased sweating) can occur when anticholinergic drugs, such as solifenacin succinate, are used in a hot environment.

Patients should be informed that solifenacin may produce angio-oedema, which could result in life-threatening airway obstruction. Patients should be advised to promptly discontinue solifenacin therapy and seek immediate attention if they experience oedema of the tongue or laryngopharynx, or difficulty in breathing.

#### ▶ Renal Impairment

##### *Tamsulosin Hydrochloride*

Patients with renal impairment do not require an adjustment in tamsulosin hydrochloride dosing. However, patients with end-stage renal disease ( $CL_{cr} < 10$  mL/min/1.73 m<sup>2</sup>) have not been studied.

##### *Solifenacin Succinate*

Solifenacin succinate should be used with caution in patients with renal impairment. There is a 2.1-fold increase in AUC and 1.6-fold increase in  $t_{1/2}$  of solifenacin in patients with severe renal impairment. Doses of solifenacin greater than 5 mg are not recommended in patients with severe renal impairment ( $CL_{cr} < 30$  mL/min).

#### ▶ Hepatic Impairment

##### *Tamsulosin Hydrochloride*

Patients with moderate hepatic impairment do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic impairment.

##### *Solifenacin Succinate*

Solifenacin succinate should be used with caution in patients with reduced hepatic function. There is a 2-fold increase in the  $t_{1/2}$  and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment. Doses of solifenacin greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin succinate tablets are not recommended for patients with severe hepatic impairment (Child-Pugh C).

#### ▶ Pregnancy

##### *Tamsulosin Hydrochloride*

##### Teratogenic Effects, Pregnancy Category B

Tamsulosin hydrochloride is not indicated for use in women.

##### *Solifenacin Succinate*

##### Pregnancy Category C

There are no adequate and well-controlled studies of solifenacin in pregnant women.

Because animal reproduction studies are not always predictive of human response, solifenacin tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

##### Labor and Delivery

The effect of solifenacin succinate on labour and delivery in humans has not been studied.

#### ▶ Lactation

##### *Tamsulosin Hydrochloride*

Tamsulosin hydrochloride is not indicated for use in women.

### *Solifenacin Succinate*

It is not known whether solifenacin is excreted in human milk. Because many drugs are excreted in human milk, solifenacin succinate should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue solifenacin in nursing mothers.

#### ▶ Paediatric Use

### *Tamsulosin Hydrochloride*

Tamsulosin hydrochloride is not indicated for use in paediatric populations.

Efficacy and positive benefit/risk of tamsulosin hydrochloride was not demonstrated in two studies conducted in patients 2 years to 16 years of age with elevated detrusor leak point pressure ( $>40$  cm H<sub>2</sub>O) associated with a known neurological disorder (e.g. spina bifida). Patients in both studies were treated on a weight-based mg/kg schema (0.025 mg, 0.05 mg, 0.1 mg, 0.2 mg, or 0.4 mg tamsulosin hydrochloride) for the reduction in detrusor leak point pressure below 40 cm H<sub>2</sub>O. In a randomized, double-blind, placebo-controlled, 14-week, pharmacokinetic, safety and efficacy study in 161 patients, no statistically significant difference in the proportion of responders was observed between groups receiving tamsulosin hydrochloride and placebo. In an open-label, 12-month safety study, 87 patients were treated with tamsulosin hydrochloride. The most frequently reported adverse events ( $\geq 5\%$ ) from the pooled data of both studies were urinary tract infection, vomiting, pyrexia, headache, nasopharyngitis, cough, pharyngitis, influenza, diarrhoea, abdominal pain, and constipation.

### *Solifenacin Succinate*

The safety and effectiveness of solifenacin in paediatric patients has not been established.

#### ▶ Geriatric Use

### *Tamsulosin Hydrochloride*

Of the total number of subjects (1,783) in clinical studies of tamsulosin, 36% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and the other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### *Solifenacin Succinate*

In placebo-controlled clinical studies, similar safety and effectiveness were observed between older (623 patients aged  $\geq 65$  years and 189 patients aged  $\geq 75$  years) and younger patients (1,188 patients aged  $< 65$  years) treated with solifenacin succinate. Multiple dose studies of solifenacin succinate in elderly volunteers (aged 65 to 80 years) showed that  $C_{max}$ , AUC and  $t_{1/2}$  values were 20 to 25% higher as compared to the younger volunteers (aged 18 to 55 years).

## Undesirable Effects

#### ▶ Tamsulosin Hydrochloride

### *Clinical Trials Experience*

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The incidence of treatment-emergent adverse events has been ascertained from six short-term US and European placebo-controlled clinical trials in which daily doses of 0.1-0.8 mg tamsulosin hydrochloride were used. These studies evaluated safety in 1,783 patients treated with tamsulosin hydrochloride capsules and

798 patients administered placebo. Table 2 summarizes the treatment-emergent adverse events that occurred in  $\geq 2\%$  of patients receiving either tamsulosin hydrochloride capsules 0.4 mg or 0.8 mg and at an incidence numerically higher than that in the placebo group during two 13-week US trials conducted in 1,487 men.

Table 3: Treatment-emergent<sup>1</sup> adverse events occurring in  $\geq 2\%$  of tamsulosin hydrochloride capsules or placebo patients in two U.S. short-term placebo-controlled clinical studies

Body System/ Adverse Event	Tamsulosin Hydrochloride Capsules Groups		Placebo
	0.4 mg n=502	0.8 mg n=492	n=493
Body As a Whole Headache	97 (19.3%)	104 (21.1%)	99 (20.1%)
Infection <sup>2</sup>	45 (9.0%)	53 (10.8%)	37 (7.5%)
Asthenia	39 (7.8%)	42 (8.5%)	27 (5.5%)
Back pain	35 (7.0%)	41 (8.3%)	27 (5.5%)
Chest pain	20 (4.0%)	20 (4.1%)	18 (3.7%)
Nervous System Dizziness	75 (14.9%)	84 (17.1%)	50 (10.1%)
Somnolence	15 (3.0%)	21 (4.3%)	8 (1.6%)
Insomnia	12 (2.4%)	7 (1.4%)	3 (0.6%)
Libido decreased	5 (1.0%)	10 (2.0%)	6 (1.2%)
Respiratory System Rhinitis <sup>3</sup>	66 (13.1%)	88 (17.9%)	41 (8.3%)
Pharyngitis	29 (5.8%)	25 (5.1%)	23 (4.7%)
Cough increased	17 (3.4%)	22 (4.5%)	12 (2.4%)
Sinusitis	11 (2.2%)	18 (3.7%)	8 (1.6%)
Digestive System Diarrhoea	31 (6.2%)	21 (4.3%)	22 (4.5%)
Nausea	13 (2.6%)	19 (3.9%)	16 (3.2%)
Tooth disorder	6 (1.2%)	10 (2.0%)	7 (1.4%)
Urogenital System Abnormal ejaculation	42 (8.4%)	89 (18.1%)	1 (0.2%)
Special Senses Blurred vision	1 (0.2%)	10 (2.0%)	2 (0.4%)

<sup>1</sup> A treatment-emergent adverse event was defined as any event satisfying one of the following criteria:  
The adverse event occurred for the first time after initial dosing with double-blind study medication.  
The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment; or  
The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.

<sup>2</sup> Coding preferred terms also include cold, common cold, head cold, flu, and flu-like symptoms.

<sup>3</sup> Coding preferred terms also include nasal congestion, stuffy nose, runny nose, sinus congestion, and hay fever.

### *Signs and Symptoms of Orthostasis*

In the two US studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4 mg group, 17% of patients (84 of 492) in the 0.8 mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported by 0.6% of patients (3 of 502) in the 0.4 mg group, 1% of patients (5 of 492) in the 0.8 mg group, and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of  $\geq 20$  mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure  $\geq 10$  mmHg upon standing, with the standing diastolic blood pressure  $< 65$  mmHg during the orthostatic test; (3) an increase in pulse rate of  $\geq 20$  bpm upon standing with a standing pulse rate  $\geq 100$  bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received tamsulosin hydrochloride 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received tamsulosin hydrochloride 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8 mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the tamsulosin hydrochloride 0.4 mg once-daily group, 92 of the 491 patients (19%) in the tamsulosin hydrochloride 0.8 mg once-daily group, and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in tamsulosin hydrochloride-treated patients than in placebo recipients, there is a potential risk of syncope.

### Abnormal Ejaculation

Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation, and ejaculation decrease. As shown in Table 2, abnormal ejaculation was associated with tamsulosin hydrochloride administration and was dose-related in the US studies. Withdrawal from these clinical studies of tamsulosin hydrochloride because of abnormal ejaculation was also dose-dependent, with 8 of 492 patients (1.6%) in the 0.8 mg group and no patients in the 0.4 mg or placebo groups discontinuing treatment due to abnormal ejaculation.

### Laboratory Tests

No laboratory test interactions with tamsulosin hydrochloride are known. Treatment with tamsulosin hydrochloride for up to 12 months had no significant effect on prostate-specific antigen (PSA).

### Postmarketing Experience

The following adverse reactions have been identified during post-approval use of tamsulosin hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to tamsulosin hydrochloride. Allergic-type reactions such as skin rash, urticaria, pruritus, angioedema, and respiratory symptoms have been reported with positive rechallenge in some cases. Priapism has been reported rarely. Infrequent reports of dyspnoea, palpitations, hypotension, atrial fibrillation, arrhythmia, tachycardia, skin desquamation, including reports of Stevens-Johnson syndrome, erythema multiforme, dermatitis exfoliative, constipation, vomiting, dry mouth, visual impairment, and epistaxis have been received during the postmarketing period. During cataract and glaucoma surgery, a variant of small pupil syndrome known as intraoperative floppy iris syndrome (IFIS) has been reported in association with  $\alpha_1$ -blocker therapy.

### ▶ Solifenacin Succinate

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Solifenacin succinate has been evaluated for safety in 1,811 patients in randomized, placebo-controlled trials. Expected adverse reactions of antimuscarinic agents are dry mouth, constipation, blurred vision (accommodation abnormalities), urinary retention, and dry eyes. The incidence of dry mouth and constipation in patients treated with solifenacin succinate was higher in the 10 mg compared to the 5 mg dose group.

In the four 12-week double-blind clinical trials, severe faecal impaction, colonic obstruction and intestinal obstruction were reported in one patient each, all in the solifenacin succinate 10 mg group. Angioneurotic oedema has been reported in one patient taking solifenacin succinate 5 mg. Compared to 12 weeks of treatment with solifenacin succinate, the incidence and severity of adverse reactions were similar in patients who remained on drug for up to 12 months.

The most frequent adverse reaction leading to study discontinuation was dry mouth (1.5%). Table 4 lists the rates of identified adverse reactions, derived from all reported adverse events, in randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with solifenacin succinate 5 or 10 mg once daily for up to 12 weeks.

**Table 4: Percentages of patients with identified adverse reactions, derived from all adverse events exceeding the placebo rate and reported by 1% or more patients in combined pivotal studies**

	Placebo (%)	Solifenacin Succinate 5 mg (%)	Solifenacin Succinate 10 mg (%)
Number of Patients	1,216	578	1,233

Gastrointestinal Disorders			
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Abdominal pain upper	1.0	1.9	1.2
Vomiting NOS	0.9	0.2	1.1
Infections and Infestations			
Urinary tract infection NOS	2.8	2.8	4.8
Influenza	1.3	2.2	0.9
Pharyngitis NOS	1.0	0.3	1.1
Nervous System Disorders			
Dizziness	1.8	1.9	1.8
Eye Disorders			
Vision blurred	1.8	3.8	4.8
Dry eyes NOS	0.6	0.3	1.6
Renal and Urinary Disorders			
Urinary retention	0.6	0	1.4
General Disorders and Administration Site Conditions			
Oedema lower limb	0.7	0.3	1.1
Fatigue	1.1	1.0	2.1
Psychiatric Disorders			
Depression NOS	0.8	1.2	0.8
Respiratory, Thoracic and Mediastinal Disorders			
Cough	0.2	0.2	1.1
Vascular Disorders			
Hypertension NOS	0.6	1.4	0.5

*Postmarketing Experience*

Because these spontaneously reported events are from the worldwide postmarketing experience, the

frequency of events and the role of solifenacin in their causation cannot be reliably determined.

The following events have been spontaneously reported in association with solifenacin use in worldwide postmarketing experience.

*General:* peripheral oedema, hypersensitivity reactions, including angio-oedema with airway obstruction, rash, pruritus, urticaria, and anaphylactic reaction

*Central Nervous:* headache, confusion, hallucinations, delirium and somnolence

*Cardiovascular:* QT prolongation; *torsades de pointes*, atrial fibrillation, tachycardia, palpitations

*Hepatic:* liver disorders, mostly characterized by abnormal liver function tests, AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (gamma-glutamyl transferase)

*Renal:* renal impairment

*Metabolism and Nutrition Disorders:* decreased appetite, hyperkalaemia

*Dermatologic:* exfoliative dermatitis and erythema multiforme

*Eye Disorders:* glaucoma

*Gastrointestinal Disorders:* gastro-oesophageal reflux disease and ileus

*Respiratory, Thoracic and Mediastinal Disorders:* dysphonia

*Musculoskeletal and Connective Tissue Disorders:* muscular weakness

If you experience any side effects, talk to your doctor or pharmacist or write to [drugsafety@cipla.com](mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects, you can help provide more information on the safety of this product.

## Overdosage

### ▶ Tamsulosin Hydrochloride

Should overdosage of tamsulosin hydrochloride capsules lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein-bound; therefore, dialysis is unlikely to be of benefit.

### ▶ Solifenacin Succinate

Overdosage with solifenacin can potentially result in severe anticholinergic effects and should be treated accordingly. The highest dose ingested in an accidental overdose of solifenacin succinate was 280 mg in a 5-hour period. This case was associated with mental status changes. Some cases reported a decrease in the level of consciousness.

Intolerable anticholinergic side effects (fixed and dilated pupils, blurred vision, failure of heel-to-toe exam, tremors and dry skin) occurred on day 3 in normal volunteers taking 50 mg daily (5 times the maximum recommended therapeutic dose) and resolved within 7 days following discontinuation of drug.

In the event of overdose with solifenacin, treat with gastric lavage and appropriate supportive measures. ECG monitoring is also recommended.

## Storage And Handling Instructions

Store at 25°C.

## Packaging Information

DUOFLO Combipack: Available as a combipack blister containing 10 Tamsulosin Hydrochloride Modified-release Capsules 400 mcg and 10 Solifenacin Succinate tablets 5 mg.

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# DUOFLO Combipack

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