SOLIDAY Tablets (Solifenacin succinate)

Composition

SOLIDAY 5 Tablets

Each film coated tablet contains:

Solifenacin Succinate.....5 mg

Colours: Ferric Oxide USP-NF Red & Titanium Dioxide IP

SOLIDAY 10 Tablets

Each film coated tablet contains:

Solifenacin Succinate.....10 mg

Colours: Ferric Oxide USP-NF Yellow & Titanium Dioxide IP

Dosage Form

Tablet

Pharmacology

Pharmacodynmics

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 three 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 analyzed 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

Absorption

After oral administration of solifenacin succinate to healthy volunteers, peak plasma levels (C_{max}) of solifenacin are reached within 3 to 8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/mL for the 5 mg 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 $\propto_1$-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 ^{14}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 to 68 hours.

Indications

SOLIDAY is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Dosage and Administration

Dosing Information

The recommended dose of SOLIDAY tablets is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.

SOLIDAY tablets should be taken with water and swallowed whole. SOLIDAY tablets can be administered with or without food.

Dose Adjustment in Patients with Renal Impairment

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

Dose Adjustment in Patients with Hepatic Impairment

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

Dose Adjustment in Patients Taking CYP3A4 Inhibitors

When administered with potent CYP3A4 inhibitors such as ketoconazole, a daily dose of SOLIDAY tablets greater than 5 mg is not recommended.

Contraindications

SOLIDAY tablets are 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

Angio-oedema 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

SOLIDAY tablets, 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

SOLIDAY tablets, 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

SOLIDAY tablets 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

Potent CYP3A4 Inhibitors

Following the administration of 10 mg of solifenacin succinate in the presence of 400 mg of ketoconazole once daily for 21 days, 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

In a crossover study, subjects received a single oral dose of warfarin 25 mg on the tenth day of dosing with either solifenacin 10 mg or matching placebo once daily for 16 days. For R-warfarin, when it was co-administered with solifenacin, the mean C_{max} increased by 3% and AUC decreased by 2%. For S-warfarin, when it was co-administered with solifenacin, the mean C_{max} and AUC increased by 5% and 1%, respectively.

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 estradiol/levonorgestrel).

Digoxin

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

Information for Patients

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

SOLIDAY tablets 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 t1/2 of solifenacin in patients with severe renal impairment Doses of SOLIDAY tablets greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr} <30 mL/min).

Hepatic Impairment

SOLIDAY tablets should be used with caution in patients with hepatic impairment. There is a 2-fold increase in the t1/2 and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment. Doses of SOLIDAY tablets greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). SOLIDAY tablets are not recommended for patients with severe hepatic impairment (Child-Pugh C).

Gender

The pharmacokinetics of solifenacin is not significantly influenced by gender.

Pregnancy

Pregnancy Category C

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

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

Labour and Delivery

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

Lactation

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 SOLIDAY tablets in nursing mothers.

Paediatric Use

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

Geriatric Use

In placebo-controlled clinical studies, similar safety and effectiveness were observed between older (623 patients aged ≥65 years and 189 patients aged ≥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

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 2 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 2: 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	1216	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 worldwide postmarketing experience. The frequency of events and the role of solifenacin in their causation cannot be reliably determined:

The following events have been 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

Overdosage

Overdosage with solifenacin succinate 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 (five times the maximum recommended therapeutic dose) and resolved within 7 days following discontinuation of the drug.

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

Storage and Handling Instructions

Store below 30°C.

Packaging Information

SOLIDAY 5 Tablets …….. pack of 10 tablets

SOLIDAY 10 Tablets ……...pack of 10 tablets

Last Updated: March 2020

Last Reviewed: April 2020