Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Solifenacin succinate/Tamsulosin hydrochloride Clonmel 6 mg/0.4 mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 6 mg solifenacin succinate, corresponding to 4.5 mg solifenacin and 0.4 mg tamsulosin hydrochloride, corresponding to 0.37 mg tamsulosin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet

Each tablet is red film-coated, round, biconvex, approximately 9 mm in diameter and debossed with "T7S" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology
Adult males, including elderly
One Solifenacin/Tamsulosin Clonmel tablet (6 mg/0.4 mg) once daily taken orally with or without food. The maximum daily dose is one Solifenacin/Tamsulosin Clonmel tablet (6 mg/0.4 mg).

Special Populations
Renal impairment
The effect of renal impairment on the pharmacokinetics of Solifenacin/Tamsulosin Clonmel has not been studied. However, the effect on the pharmacokinetics of the individual active substances is well known (see section 5.2). Solifenacin/Tamsulosin Clonmel 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 Clonmel tablet (6 mg/0.4 mg) (see section 4.4).

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of Solifenacin/Tamsulosin Clonmel has not been studied. However, the effect on the pharmacokinetics of the individual active substances is well known (see section 5.2). Solifenacin/Tamsulosin Clonmel 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 Clonmel tablet (6 mg/0.4 mg). In patients with severe hepatic impairment (Child-Pugh score > 9), the use of Solifenacin/Tamsulosin Clonmel is contraindicated (see section 4.3).

Moderate and strong inhibitors of cytochrome P450 3A4
The maximum daily dose of Solifenacin/Tamsulosin Clonmel should be limited to one tablet (6 mg/0.4 mg). Solifenacin/Tamsulosin Clonmel should be used with caution in patients treated simultaneously with moderate or strong CYP3A4 inhibitors, e.g. verapamil, ketoconazole, ritonavir, nelfinavir, itraconazole (see section 4.5).

Paediatric population
There is no relevant indication for use of Solifenacin/Tamsulosin Clonmel in children and adolescents.

Method of administration

The tablet must be swallowed whole, intact without biting or chewing. Do not crush the tablet.

4.3 Contraindications

- Patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1,
- Patients undergoing haemodialysis (see section 5.2),
- Patients with severe hepatic impairment (see section 5.2),
- Patients with severe renal impairment who are also treated with a strong cytochrome P450 (CYP) 3A4 inhibitor, e.g., ketoconazole (see section 4.5),
- Patients with moderate hepatic impairment who are also treated with a strong CYP3A4 inhibitor, e.g., ketoconazole (see section 4.5),
- 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.

4.4 Special warnings and precautions for use

Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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, Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride in patients for whom cataract or glaucoma surgery is scheduled is not recommended. Discontinuing treatment with Solifenacin succinate/Tamsulosin hydrochloride 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 or have been treated with Solifenacin succinate/Tamsulosin hydrochloride in order to ensure that appropriate measures will be in place to manage IFIS during surgery.

Solifenacin succinate/Tamsulosin hydrochloride should be used with caution in combination with moderate and strong inhibitors of CYP3A4 (see section 4.5) 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.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of 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 Solifenacin succinate/Tamsulosin hydrochloride, 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 succinate/Tamsulosin hydrochloride should be used with caution in combination with strong CYP3A4 inhibitors.
Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 alpha1-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.

4.6 Fertility, pregnancy and lactation

Fertility
The effect of Solifenacin succinate/Tamsulosin hydrochloride on fertility has not been established. Animal studies with solifenacin or tamsulosin do not indicate harmful effects on fertility and early embryonic development (see section 5.3).

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 Breast-feeding
Solifenacin succinate/Tamsulosin hydrochloride is not indicated for use in women.

4.7 Effects on ability to drive and use machines

No studies on the effects of Solifenacin succinate/Tamsulosin hydrochloride on the ability to drive or use machines have been performed. However, patients should be informed about the possible occurrence of dizziness, blurred vision, fatigue and uncommonly, somnolence, which may negatively affect the ability to drive or use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Solifenacin succinate/Tamsulosin hydrochloride may cause anticholinergic undesirable effects of, in general, mild to moderate severity. The most frequently reported adverse reactions during the clinical studies performed for the development of Solifenacin succinate/Tamsulosin hydrochloride were dry mouth (9.5%), followed by constipation (3.2%) and dyspepsia (including abdominal pain; 2.4%). Other common undesirable effects are dizziness (including vertigo; 1.4%), vision blurred (1.2%), fatigue (1.2%), and ejaculation disorder (including retrograde ejaculation; 1.5%). Acute urinary retention (0.3%, uncommon) is the most serious adverse drug reaction that has been observed during treatment with Solifenacin succinate/Tamsulosin hydrochloride in clinical studies.

Tabulated list of adverse reactions
In the table below the 'Solifenacin succinate/Tamsulosin hydrochloride frequency' column reflects adverse drug reactions that have been observed during the double-blind clinical studies performed for the development of Solifenacin succinate/Tamsulosin hydrochloride (based on reports of treatment-related adverse events, which have been reported by at least two patients and occurred with a frequency higher than for placebo in the double-blind studies).

The columns 'solifenacin frequency' and 'tamsulosin frequency' reflect adverse drug reactions (ADRs) previously reported with one of the individual components (as presented in the Summary of Product Characteristics (SmPCs) of solifenacin 5 and 10 mg and tamsulosin 0.4 mg respectively) that may also occur when receiving Solifenacin succinate/Tamsulosin hydrochloride (some of these have not been observed during the clinical development program of Solifenacin succinate/Tamsulosin hydrochloride).

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class (SOC)/Preferred Term (PT)	ADR frequency observed during development of Solifenacin succinate/ Tamsulosin hydrochloride	ADR frequency observed with the individual substances	
		Solifenacin 5mg and 10 mg[#]	Tamsulosin 0.4mg[#]
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	Common	Rare*	Common
Somnolence		Uncommon	
Dysgeusia		Uncommon	
Headache		Rare*	Uncommon
Syncope			Rare
Eye disorders			
Vision blurred	Common	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	Common	Very common	
Dyspepsia	Common	Common	
Constipation	Common	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	Uncommon	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***	Uncommon	Rare	
Difficulty in micturition		Uncommon	
Renal impairment		Not known*	
Reproductive system and breast disorders			
Ejaculation disorders including retrograde ejaculation and ejaculation failure	Common		Common
Priapism			Very rare
General disorders and administration site conditions			
Fatigue	Common	Uncommon	
Peripheral oedema		Uncommon	
Asthenia			Uncommon

#: The ADRs from solifenacin and tamsulosin included in this table are the ADRs listed in the summary of product characteristics of both products.
*: from post-marketing reporting. Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of solifenacin or tamsulosin and their causation cannot be reliably determined.
**: from post-marketing reporting, observed during cataract and glaucoma surgery.
***: see section 4.4 Special warnings and precautions for use.

Long –term safety of Solifenacin succinate/Tamsulosin hydrochloride
The profile of undesirable effects seen with treatment up to 1 year was similar to that observed in the 12-week studies. The product is well-tolerated and no specific adverse reactions have been associated with long-term use.

Description of selected adverse reactions
For urinary retention see section 4.4 Special warnings and precautions for use.

Elderly
The therapeutic indication of Solifenacin succinate/Tamsulosin hydrochloride, moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with BPH, is a disease affecting elderly men. The clinical development of Solifenacin succinate/Tamsulosin hydrochloride has been performed in patients 45 to 91 years of age, with an average age of 65 years. Adverse reactions in the elderly population were similar to the younger population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
Overdosage with the combination of solifenacin and tamsulosin can potentially result in severe anticholinergic effects plus acute hypotension. The highest dose taken accidentally during a clinical study corresponded to 126 mg of solifenacin succinate and 5.6 mg of tamsulosin hydrochloride. This dose was well-tolerated, with mild dry mouth for 16 days as the only reported adverse event.

Treatment
In the event of overdose with solifenacin and tamsulosin, 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 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. Beta-blockers should be used with caution, since the concomitant overdose with tamsulosin 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., hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e., myocardial ischaemia, arrhythmia, congestive heart failure).

Acute hypotension, which can occur after overdosage due to the tamsulosin component, should be treated symptomatically. Hemodialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha-adrenoceptor antagonists, ATC code: G04CA53

Mechanism of action
Solifenacin succinate/Tamsulosin hydrochloride is 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 alpha$_1$-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.

Pharmacodynamic effects
Solifenacin succinate/Tamsulosin hydrochloride tablets consist of two active substances with independent and complementary effects in LUTS associated with BPH, with storage symptoms:
Solifenacin ameliorates storage function problems related to non-neuronally released acetylcholine activating M3-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.

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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride was non-inferior to tamsulosin OCAS on total IPSS ($p < 0.001$), as expected.

5.2 Pharmacokinetic properties

Solifenacin succinate/Tamsulosin hydrochloride
The information below presents the pharmacokinetic parameters after multiple dosing of Solifenacin succinate/Tamsulosin hydrochloride.
A multiple dose relative bioavailability study demonstrated that the administration of Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride, 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride, the $t_{1/2}$ 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 succinate/Tamsulosin hydrochloride resulted in a 60% increase in C_{max} and a 63% increase in AUC for solifenacin, while for tamsulosin C_{max} increased by 115% 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 succinate/Tamsulosin hydrochloride:

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 α1-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 α1-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-ethoxyphenoxy acetic acid.

Characteristics in specific groups of patients
Elderly
In the clinical pharmacology and biopharmaceutical studies, the age of the subjects varied between 19 and 79 years. After Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride can be used in elderly patients.

Renal impairment
Solifenacin succinate/Tamsulosin hydrochloride
Solifenacin succinate/Tamsulosin hydrochloride 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 succinate/Tamsulosin hydrochloride 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 $t_{1/2}$ 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 α1-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 succinate/Tamsulosin hydrochloride
Solifenacin succinate/Tamsulosin hydrochloride can be used in patients with mild to moderate hepatic impairment, but is contraindicated in patients with severe hepatic impairment.

The pharmacokinetics of Solifenacin succinate/Tamsulosin hydrochloride 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 $t_{½}$ 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.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with Solifenacin succinate/Tamsulosin hydrochloride. Solifenacin and tamsulosin have been extensively evaluated individually in animal toxicity tests and findings were consistent with the known pharmacological actions. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential and do not raise a concern for potentiation or synergism of adverse effects when solifenacin and tamsulosin are combined.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Calcium hydrogen phosphate
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Iron oxide red (E172)
Magnesium stearate (E470b)
Macrogol, high-molecular mass
Silica, colloidal anhydrous

Tablet coating
Hypromellose (E464)
Iron oxide red (E172)
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 °C

6.5 Nature and contents of container

oPA/Alu/PVC/Alu blisters containing 10, 14, 20, 28, 30, 50, 56, 60, 90, 100 or 200 modified-release tablets or oPA/Alu/PVC/Alu perforated unit-dose blisters containing 10 x 1, 14 x 1, 20 x 1, 28 x 1, 30 x 1, 50 x 1, 56 x 1, 60 x 1, 90 x 1, 100 x 1 or 200 x 1 modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/351/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th July 2023

10 DATE OF REVISION OF THE TEXT

March 2024