AUSTRALIAN PRODUCT INFORMATION

UROREC® (SILODOSIN) CAPSULES

1. NAME OF THE MEDICINE

Silodosin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

UROREC hard gelatin capsules contain either 4 mg or 8 mg of silodosin.

3. PHARMACEUTICAL FORM

UROREC 4 mg is presented as yellow, opaque, hard gelatin capsules.

UROREC 8 mg is presented as white, opaque, hard gelatin capsules.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

UROREC is indicated for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men.

4.2. Dose and Method of Administration

Dosage

The recommended dose is one capsule of UROREC 8 mg daily.

Method of Administration

A capsule should be taken with food, preferably at the same time every day. It should not be broken or chewed but swallowed whole, preferably with a glass of water.

Dosage Adjustment

For special patient populations, one capsule of UROREC 4 mg daily is recommended (see below).

Use in the Elderly

No dose adjustment is required in the elderly.

Use in Renal Impairment

No dose adjustment is required for patients with mild renal impairment ($CL_{CR} \geq 60$ to ≤ 89 ml/min; eGFR ≥ 60 to ≤ 89 ml/min/1.73 m^2; CKD stage G2).

A starting dose of 4 mg once daily is recommended in patients with moderate renal impairment ($CL_{CR} \geq 30$ to ≤ 59 ml/min; eGFR ≥ 30 to ≤ 59 ml/min/1.73 m^2; CKD stage G3a and G3b), caution is recommended if the dose is increased to 8 mg, based on the individual patient's response (see *section 5.2. Pharmacokinetic Properties – Use in Renal Impairment*).

The use in patients with severe renal impairment ($CL_{CR} < 30$ ml/min; eGFR < 30 ml/min/1.73m^2; CKD stage G4 and G5) is not recommended (see *section 4.4. Special Warnings and Precautions for Use*).

Use in Hepatic Impairment

No dose adjustment is required for patients with mild to moderate hepatic impairment. As no data are available, the use in patients with severe hepatic impairment is not recommended (see *section 4.4. Special Warnings and Precautions for Use*).

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special Warnings and Precautions for Use

Identified Precautions

Orthostatic Effects

The incidence of orthostatic effects with silodosin is very low. However, a reduction in blood pressure can occur in individual patients, leading in rare cases to syncope. At the first signs of orthostatic hypotension (such as postural dizziness), the patient should sit or lie down until the symptoms have disappeared. In patients with orthostatic hypotension, treatment with silodosin is not recommended.

Carcinoma of the Prostate

Since BPH and prostate carcinoma may present the same symptoms and can co-exist, patients thought to have BPH should be examined prior to starting therapy with silodosin, to rule out the presence of carcinoma of the prostate. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

Retrograde Ejaculation

Treatment with silodosin leads to a decrease in the amount of semen released during orgasm that may temporarily affect male fertility. This effect disappears after discontinuation of silodosin (see *section 4.8. Adverse Effects (Undesirable Effects)*).

Intraoperative Floppy Iris Syndrome (IFIS)

IFIS (a variant of small pupil syndrome) has been observed during cataract surgery in a significant proportion of patients on α_1-blockers or previously treated with α_1-blockers. This may lead to increased procedural complications during the operation and an increase in post-operative complications.

The initiation of therapy with silodosin is not recommended in patients for whom cataract surgery is scheduled. The benefit and duration of stopping the therapy prior to cataract surgery has not yet been established.

During pre-operative assessment, eye surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have ever been treated with silodosin, in order to ensure that appropriate measures will be in place to minimise the effects of peri-operative IFIS.

Concomitant Use with Other Alfa-Blockers

Since there is inadequate information about the safe use of silodosin in association with other α-adrenoreceptor antagonists, this use is not recommended.

Use in Hepatic Impairment

Since no data are available in patients with severe hepatic impairment, the use of silodosin in these patients is not recommended (see *section 4.2. Dose and Method of Administration*, see also *section 5.2. Pharmacokinetic Properties – Special Populations*).

Use in Renal Impairment

Since only limited experience exists in patients with moderate renal impairment ($CL_{CR} \geq 30$ to $\leq$ 59 ml/min; eGFR ≥ 30 to ≤ 59 ml/min/1.73 m^2; CKD stage G3a and G3b) (n=35), a lower starting dose of 4 mg is recommended, caution should be exercised if the dose is increased to 8 mg once daily, based on the individual patient's response.

Since there are no clinical safety data in patients with severe renal impairment ($CL_{CR} <$ 30 ml/min; eGFR < 30 ml/min/1.73m^2; CKD stage G4 and G5) the use of silodosin in these patients is not recommended (see *section 4.2. Dose and Method of Administration*, see also *section 5.2. Pharmacokinetic Properties – Special Populations*).

Use in the Elderly

Exposure to silodosin and its main metabolites does not change significantly with age, even in subjects of age over 75 years. Orthostatic hypotension occurs more commonly in patients aged > 75 years although it is usually mild and resolves with continued treatment.

Paediatric Use

Silodosin has not been evaluated in patients less than 18 years of age. UROREC is not indicated for use in the paediatric population.

Effects on Laboratory Tests

No data available.

4.5. Interactions with Other Medicines and Other Forms of Interactions

Silodosin is metabolised extensively, mainly via CYP3A4, alcohol dehydrogenase and UGT2B7. Co-administration of silodosin with agents that interfere with these enzymes may increase circulating levels of unchanged silodosin. Silodosin is also a substrate for P-glycoprotein and exposure may be enhanced by P-glycoprotein inhibitors. Substances that inhibit (such as ketoconazole, itraconazole, ritonavir or cyclosporine) or induce (such as rifampicin, barbiturates, carbamazepine, phenytoin) these enzymes and transporters may affect the plasma concentrations of silodosin and its active metabolite.

Alpha-Blockers

There is inadequate information about the safe use of silodosin in association with other α-adrenoreceptor antagonists. Consequently, the concomitant use of other α-adrenoreceptor antagonists is not recommended.

CYP3A4 Inhibitors

In an interaction study, a 3.7-fold increase in maximum silodosin plasma concentrations and a 3.1-fold increase in silodosin exposure (i.e. AUC) were observed with concurrent administration of a potent CYP3A4 inhibitor (ketoconazole 400 mg). Concomitant use with potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir or cyclosporine) is not recommended.

When silodosin was co-administered with a CYP3A4 inhibitor of moderate potency such as diltiazem, an increase in silodosin AUC of approximately 30 % was observed, but C_{max} and half-life were not affected. This change is clinically not relevant and no dose adjustment is required.

Strong P-Glycoprotein (P-Gp) Inhibitors

Since *in vitro* studies indicated that silodosin is a P-gp substrate, inhibition of P-gp may lead to increased silodosin concentrations. Therefore, coadministration with strong P-gp inhibitors is not recommended.

PDE-5 Inhibitors

Minimal pharmacodynamic interactions have been observed between silodosin and maximum doses of sildenafil or tadalafil. In a placebo-controlled study in 24 subjects 45-78 years of age receiving silodosin, the co-administration of sildenafil 100 mg or tadalafil 20 mg induced no clinically meaningful mean decreases in systolic or diastolic blood pressure, as assessed by orthostatic tests (standing *versus* supine). In the subjects over 65 years, the mean decreases at the various time points were between 5 and 15 mmHg (systolic) and 0 and 10 mmHg (diastolic). Positive orthostatic tests were only slightly more common during co-administration; however, no symptomatic orthostasis or dizziness occurred. Patients taking PDE-5 inhibitors concomitantly with silodosin should be monitored for possible adverse reactions.

Antihypertensives

In the clinical study program, many patients were on concomitant antihypertensive therapy (mostly agents acting on the rennin-angiotensin system, beta-blockers, calcium antagonists and diuretics) without experiencing an increase in the incidence of orthostatic hypotension. Nevertheless, caution should be exercised when starting concomitant use with antihypertensives and patients should be monitored for possible adverse reactions.

Digoxin

Steady state levels of digoxin, a substrate of P-glycoprotein, were not significantly affected by co-administration with silodosin 8 mg once daily. No dose adjustment is required.

4.6. Fertility, Pregnancy and Lactation

Effects on Fertility

In male rats, decreased fertility was observed from exposures which were approximately twice the exposure at the maximum recommended human dose. The observed effect was reversible.

In clinical studies, the occurrence of ejaculation with reduced or no semen has been observed during treatment with silodosin, due to the pharmacodynamic properties of silodosin. Before starting treatment, the patient should be informed that this effect may occur, temporarily affecting male fertility.

Use in Pregnancy

Category B3

Silodosin is not indicated for use in female patients. Embryo-foetal development studies in rats and rabbits did not find evidence of teratogenic effects at doses up to 1000 mg/kg/day in rats (> 1000 times the clinical dose, based on body surface area comparisons) and 60 mg/kg/day in rabbits (2.9 times the clinical AUC at the MRHD). There were treatment-related increases in foetal losses and abortions in rabbits at doses ≥ 200 mg/kg/day (23 times the clinical AUC), which were secondary to maternotoxic effects of silodosin. As well, findings from a pre-/postnatal development study in rats indicated treatment-related impairments to development (impaired suckling and ambulation at doses ≥ 300 mg/kg/day or > 340 times the clinical dose, based on body surface area comparisons).

Use in Lactation

Silodosin is indicated for use in males only. No animal data are available on whether silodosin passes into milk.

4.7. Effects on Ability to Drive and Use Machines

UROREC has minor or moderate influence on the ability to drive and use machines. Patients should be informed about the possible occurrence of symptoms related to postural hypotension (such as dizziness) and should be cautioned about driving or operating machines until they know how silodosin will affect them.

4.8. Adverse Effects (Undesirable Effects)

Summary of the Safety Profile

The safety of silodosin has been evaluated in four Phase II-III double-blind controlled clinical studies (with 931 patients receiving silodosin 8 mg once daily and 733 patients receiving placebo) and in two long-term open-label extension phase studies. In total, 1,581 patients have received silodosin at a dose of 8 mg once daily, including 961 patients exposed for at least 6 months and 384 patients exposed for 1 year.

The most frequent adverse events reported with silodosin in placebo controlled clinical studies and during long-term use were ejaculatory disorders such as retrograde ejaculation and anejaculation (ejaculatory volume reduced or absent), with a frequency of 23%. This may temporarily affect male fertility. It is reversible within a few days upon discontinuation of treatment (see *section 4.4. Special Warnings and Precautions for Use*).

List of Adverse Events

Adverse events with incidence ≥ 1% reported in the four phase II-III placebo controlled clinical studies with silodosin 8 mg are listed by MedDRA system organ class in Table 1.

Table 1: Adverse Events for Silodosin in Four Phase II-III Studies

	Silodosin N=931	**Placebo N=733**
Gastrointestinal disorders		
Diarrhoea	19 (2.0%)	14 (1.9%)
Nervous system disorders		
Dizziness	23 (2.5%)	12 (1.7%)
Headache	24 (2.6%)	19 (2.6%)
Psychiatric disorders		
Insomnia	10 (1.1%)	0 (0.0%)
Renal and urinary disorders		
Urinary tract infection	10 (1.1%)	2 (0.3%)
Reproductive system and breast disorders		
Retrograde ejaculation	201 (21.6%)	6 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Influenza	12 (1.3%)	6 (0.8%)
Nasal congestion	13 (1.4%)	2 (0.3%)
Nasopharyngitis	16 (1.7%)	18 (2.5%)
Sinusitis	11 (1.2%)	5 (0.7%)
Vascular disorders		
Hypertension	16 (1.7%)	14 (1.9%)
Orthostatic hypotension	14 (1.5%)	8 (1.1%)

Adverse events with incidence ≥ 1% recorded in the European phase III active and placebo controlled clinical trial are listed by MedDRA system organ class in Table 2.

Table 2: Adverse Events for Silodosin in the European Phase III Trial

	Silodosin N=381	**Tamsulosin N=384**	**Placebo N=190**
Cardiac disorders			
Tachycardia	4 (1.0%)	2 (0.5%)	0 (0.0%)
Gastrointestinal disorders			
Diarrhoea	3 (0.8%)	4 (1.0%)	3 (1.6%)
Infections and infestations			
Pharyngitis	5 (1.3%)	3 (0.8%)	2 (1.1%)
Nervous system disorders			
Dizziness	8 (2.1%)	4 (1.0%)	1 (0.5%)
Headache	11 (2.9%)	21 (5.5%)	9 (4.7%)
Psychiatric disorders			
Loss of libido	4 (1.0%)	0 (0.0%)	1 (0.5%)

	Silodosin N=381	Tamsulosin N=384	Placebo N=190
Renal and urinary disorders			
Urinary tract infection	5 (1.3%)	1 (0.3%)	0 (0.0%)
Reproductive system and breast disorders			
Retrograde ejaculation	54 (14.2%)	8 (2.1%)	2 (1.1%)
Erectile dysfunction	4 (1.0%)	2 (0.5%)	2 (1.1%)
Respiratory, thoracic and mediastinal disorders			
Influenza	11 (2.9%)	15 (3.9%)	3 (1.6%)
Nasopharyngitis	5 (1.3%)	9 (2.3%)	3 (1.6%)
Rhinitis	4 (1.0%)	3 (0.8%)	1 (0.5%)
Vascular disorders			
Hypertension	8 (2.1%)	4 (1.0%)	2 (1.1%)
Orthostatic hypotension	2 (0.5%)	1 (0.3%)	0 (0.0%)

Adverse reactions reported in all clinical studies and in the worldwide post-marketing experience for which a reasonable causal relationship exists are listed by MedDRA system organ class and frequency: very common 10%; common (≥ 1% to < 10%); uncommon (≥ 0.1% to < 1%); rare (≥ 0.01% to < 0.1%); very rare (< 0.01%), not known (cannot be estimated from available data). Within each frequency grouping, the observed adverse events are presented in order of decreasing seriousness.

Immune System Disorders

Very rare: Allergic-type reactions including facial swelling, swollen tongue and pharyngeal oedema

Psychiatric Disorders

Uncommon: Libido decreased

Nervous System Disorders

Common: Dizziness

Rare: Syncope loss of consciousness

Cardiac Disorders

Uncommon: Tachycardia

Rare: Palpitations

Vascular Disorders

Common: Orthostatic hypotension**

Uncommon: Hypotension

Respiratory, Thoracic and Mediastinal Disorders

Common: Nasal congestion

Gastrointestinal Disorders

Common: Diarrhoea

Uncommon: Nausea, dry mouth

Hepatobiliary Disorders

Uncommon: Abnormal liver function tests

Skin and Subcutaneous Tissue Disorders

Uncommon: Skin rash, pruritus, urtricaria, drug eruption

Reproductive System and Breast Disorders

Very common: Ejaculatory disorders, including retrograde ejaculation, anejaculation

Uncommon: Erectile dysfunction

Injury, Poisoning and Procedural Complication

Unknown: Intraoperative Floppy Iris Syndrome*

* Intraoperative Floppy Iris Syndrome (IFIS) - IFIS has been reported during cataract surgery (see *section 4.4. Special Warnings and Precautions for Use*).

** Orthostatic hypotension - The incidence of orthostatic hypotension in placebo-controlled clinical studies was 1.2% with silodosin and 1.0% with placebo. Orthostatic hypotension may occasionally lead to syncope, (see *section 4.4. Special Warnings and Precautions for Use*).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9. Overdose

Silodosin was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose-limiting adverse reaction was postural hypotension. Should overdose of silodosin lead to hypotension, cardiovascular support has to be provided. Dialysis is unlikely to be of significant benefit since silodosin is highly (approximately 95%) protein bound.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Urologicals, alpha-adrenoreceptor antagonists, ATC code: G04CA04.

5.1. Pharmacodynamic Properties

Mechanism of Action

Silodosin is a selective antagonist of α_{1A}-adrenoreceptors primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Data from an *in vitro* study showed that silodosin has lower affinity for α_{1B}-adrenoreceptors that are primarily located in the cardiovascular system than for the α_{1A}-adrenoreceptor subtype. Blockade of α_{1A}-adrenoreceptors causes smooth muscle in these tissues to relax, thus decreasing bladder outlet resistance, without affecting detrusor smooth muscle contractility. This causes an improvement of both storage (irritative) and voiding (obstructive) symptoms (Lower urinary tract symptoms, LUTS) associated with benign prostatic hyperplasia.

Clinical Trials

A total number of 837 patients with moderate to severe symptoms of BPH (International Prostate Symptom Score, IPSS, baseline value ≥13) received silodosin 8 mg once daily in two Phase III placebo-controlled clinical studies conducted in the United States and in one placebo- and active-controlled clinical study conducted in Europe. In all studies, patients who did not respond to placebo during a 4-week placebo run-in phase were randomised to receive the study treatment. In all studies, patients treated with silodosin had a greater decrease in both storage (irritative) and voiding (obstructive) symptoms of BPH as compared to placebo as assessed after 12 weeks of treatment. Data observed in the Intent-to-treat populations of each study are shown in Table 3 below.

Table 3: Data from the Intent-to-Treat Populations from Three US and European Phase III Studies

Study	Treatment arm	IPSS Total score			IPSS Irritative symptoms		IPSS Obstructive Symptoms		IPSS Quality of Life	
		Baseline value (±SD)	Change from baseline	Difference (95 % CI) vs placebo	Change from baseline	Difference (95 % CI) vs placebo	Change from baseline	Difference (95 % CI) vs placebo	Change from baseline	Difference (95 % CI) vs placebo
US-1	Silodosin (N=233)	22 ± 5	-6.5	-2.8[1] (-3.9, -1.7)	-2.3	-0.9 (-1.4, -0.4)	-4.2	-1.9 (-2.6, -1.2)	-0.8	0.4 (0.2, 0.6)
	Placebo (N=228)	21± 5	-3.6		-1.4		-2.2		-0.4	
US-2	Silodosin (N=233)	21 ± 5	-6.3	-2.9[1] (-4.0, -1.8)	-2.4	-1.0 (-1.5, -0.6)	-3.9	-1.8 (-2.5, -1.1)	-0.9	0.5 (0.3, 0.7)
	Placebo (N=229)	21 ± 5	-3.4		-1.3		-2.1		-0.3	
EU	Silodosin (N=371)	19 ± 4	-7.0	-2.3[1] (-3.2, -1.4)	-2.5	-0.7[1] (-1.1, -0.2)	-4.5	-1.7 (-2.2, -1.1)	-1.1	-0.3 (-0.5, -0.1)
	Tamsulosin (N=376)	19 ± 4	-6.7	-2.0[1] (-2.9, -1.1)	-2.4	-0.6 (-1.1, -0.2)	-4.2	-1.4 (-2.0, -0.8)	-1.1	-0.3 (-0.5, -0.1)
	Placebo (N=185)	19 ± 4	-4.7		-1.8		-2.9		-0.8	

[1] $p < 0.001$ versus placebo

The outcomes were comparable in subgroups based on age and race.

In the active-controlled clinical study conducted in Europe, silodosin 8 mg once daily was shown to be non inferior to tamsulosin 0.4 mg once daily: the adjusted mean difference (95 % CI) in the IPSS Total Score between treatments in the per-protocol population was 0.4 (-0.4 to 1.1). The responder rate (i.e. improvement in the IPSS total score by at least 25 %) was significantly higher in the silodosin (68 %) and tamsulosin group (65 %), as compared to placebo (53 %).

In the long-term open-label extension phase of these controlled studies, in which patients received silodosin for up to 1 year, the symptom improvement induced by silodosin at week 12 of treatment was maintained over 1 year.

A centralised reading of the maximum urinary flow rate (Q_{max}) was performed in the two Phase III US placebo-controlled clinical studies. Statistically significant treatment effects on Q_{max} were noted already within 2 to 6 hours after the first dose and at the end of both studies.

Table 4: Treatment Effects from Two US Phase III Studies

Study	Drug	Mean Baseline Q_{max} (mL/sec)	Change from baseline (2-6 hours post-dose)	Change from baseline (week 12/LOCF)
US-1	Silodosin 8 mg	9.0 ± 2.6	2.7 ± 3.5 P<0.0001 vs. P	2.2 ± 4.3 p=0.006 vs. P
	Placebo	9.0 ± 2.9	0.8 ± 3.1	1.2 ± 3.8
US-2	Silodosin 8 mg	8.4 ± 2.5	2.9 ± 3.4 P=0.0494 vs. P	2.9 ± 4.5 p=0.0431 vs. P
	Placebo	8.7 ± 2.7	2.1 ± 4.3	1.9 ± 4.8

An improvement in Q_{max} was also observed at all study visits for all treatment groups in the analysis derived from the post-hoc centralised reading of the European study, but the difference from placebo did not reach the statistical significance because of a particularly high placebo response seen in this study.

Table 5: Treatment Effects from One European Phase III Study

Study	Drug	Mean Baseline Q_{max} (mL/sec)	Change from baseline (week 12/LOCF)
EU	Silodosin 8 mg	9.3 ± 2.6	3.1 – p= 0.110 vs. P
	Tamsulosin 0.4 mg	9.0 ± 2.6	3.1 – p= 0.097 vs. P
	Placebo	9.2 ± 2.9	2.4

In a Phase II dose-finding, double-blind, placebo-controlled clinical study with silodosin 4 or 8 mg once daily, a greater improvement in American Urologic Association (AUA) symptom index score was observed with silodosin 8 mg (-6.8 ± 5.8, n = 90; p = 0.0018) and silodosin 4 mg (-5.7 ± 5.5, n = 88; p = 0.0355) as compared to placebo (-4.0 ± 5.5, n = 83).

In a Phase IV clinical trial performed in Europe, with a mean baseline IPSS total score of 18.9 points, 77.1 % were responders to silodosin (as assessed by a change from baseline in the IPSS total score of at least 25 %). Approximately half of the patients reported an improvement in the most bothersome symptoms complained at baseline by the patients (i.e. nocturia, frequency, decreased stream, urgency, terminal dribbling and incomplete emptying), as assessed by the ICS-male questionnaire.

No significant reduction in supine blood pressure was observed in all clinical studies conducted with silodosin.

Silodosin 8 mg and 24 mg daily had no statistically significant effect on ECG intervals or cardiac repolarisation relative to placebo.

5.2. Pharmacokinetic Properties

The pharmacokinetics of silodosin and its main metabolites have been evaluated in adult male subjects with and without BPH after single and multiple administrations with doses ranging from 0.1 mg to 48 mg per day. The pharmacokinetics of silodosin is linear throughout this dose range.

The exposure to the main metabolite in plasma, silodosin glucuronide (KMD-3213G), at steady-state is about 3-fold that of the parent substance. Silodosin and its glucuronide reach steady-state after 3 days and 5 days of treatment, respectively.

Absorption

Silodosin administered orally is well absorbed and absorption is dose proportional. The absolute bioavailability is approximately 32 %.

An *in vitro* study with Caco-2 cells showed that silodosin is a substrate for P-glycoprotein.

Food decreases C_{max} by approximately 30 %, increases t_{max} by approximately 1 hour and has little effect on AUC.

In healthy male subjects of the target age range (n=16, mean age 55 ± 8 years) after once-a-day oral administration of 8 mg immediately after breakfast for 7 days, the following pharmacokinetic parameters were obtained: C_{max} 87 ± 51 ng/ml (sd), t_{max} 2.5 hours (range 1.0-3.0), AUC 433 ± 286 ng • h/ml.

Distribution

Silodosin has a volume of distribution of 0.81 l/kg and is approximately 95% bound to plasma proteins, while binding of silodosin glucuronide is approximately 92%. Silodosin did not distribute into blood cells under *in vitro* conditions.

Metabolism

Silodosin undergoes extensive metabolism through glucuronidation (UGT2B7), alcohol and aldehyde dehydrogenase and oxidative pathways, mainly CYP3A4. The main metabolite in plasma, the glucuronide conjugate of silodosin (KMD-3213G), that has been shown to be active *in vitro*, has an extended half-life (approximately 24 hours) and reaches plasma concentrations approximately four times higher than those of silodosin. *In vitro* data indicate that silodosin does not inhibit or induce cytochrome P450 enzyme systems.

Excretion

Following oral administration of ^{14}C-labelled silodosin, the recovery of radioactivity after 7 days was approximately 33.5 % in urine and 54.9 % in faeces. Body clearance of silodosin was approximately 0.28 l/h/kg. Silodosin is excreted mainly as metabolites, very low amounts of unchanged drug are recovered in urine. The terminal half-life of parent drug and its glucuronide is approximately 11 hours and 18 hours, respectively.

Special Populations

Use in Hepatic Impairment

In a single-dose study, the pharmacokinetics of silodosin was not altered in nine patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), compared to nine healthy subjects. Results from this study should be interpreted with caution, since enrolled patients had normal biochemistry values, indicating normal metabolic function, and they were classified as having moderate liver impairment based on ascites and hepatic encephalopathy.

The pharmacokinetics of silodosin in patients with severe hepatic impairment has not been studied.

Use in Renal Impairment

In a single-dose study, exposure to silodosin (unbound) in subjects with mild (CL_{CR} ≥ 60 to ≤ 89 ml/min; eGFR ≥ 60 to ≤ 89 ml/min/1.73 m^2; CKD stage G2) (n=8) and moderate renal impairment (CL_{CR} ≥ 30 to ≤ 59 ml/min; eGFR ≥ 30 to ≤ 59 ml/min/1.73 m^2; CKD stage G3a and G3b) (n=8) resulted, on average, in an increase of C_{max} (1.6-fold) and AUC (1.7-fold) relative to subjects with normal renal function (n=8). In subjects with severe renal impairment (CL_{CR} < 30 ml/min; eGFR < 30 ml/min/1.73m^2; CKD stage G4 and G5) (n=5) increase of exposure was 2.2-fold for C_{max} and 3.7-fold for AUC. Exposure to the main metabolites, silodosin glucuronide and KMD3293, was also increased.

Plasma level monitoring in a Phase III clinical study showed that levels of total silodosin after 4 weeks of treatment did not change in patients with mild impairment (n=70), compared to patients with normal renal function (n=155), while the levels were doubled on average in patients with moderate impairment (n=7).

A review of safety data of patients enrolled in all clinical studies does not indicate that mild renal impairment (n=487) poses an additional safety risk during silodosin therapy (such as an increase in dizziness or orthostatic hypotension) as compared to patients with normal renal function (n=955). Accordingly, no dose adjustment is required in patients with mild renal impairment. Since only limited experience exists in patients with moderate renal impairment (n=35), a lower starting dose of 4 mg is recommended, caution should be exercised if the dose is increased to 8 mg once daily, based on the individual patient's response. In patients with severe renal impairment administration of UROREC is not recommended.

5.3. Preclinical Safety Data

Genotoxicity

Silodosin was not found to be genotoxic in the *in vitro* Ames assay, mouse lymphoma assay, unscheduled DNA synthesis assay and the *in vivo* mouse micronucleus assay. A weakly positive response in two *in vitro* Chinese Hamster Lung (CHL) tests for chromosomal aberration was observed at high, cytotoxic concentrations of silodosin.

Carcinogenicity

Increase in thyroid tumours (follicular cell adenoma and carcinoma) were observed in male rats in a two-year carcinogenicity study at doses ≥ 50 mg/kg/day (5.1 times the clinical AUC at the MRHD). Chronic stimulation of TSH secretion resulting from a silodosin-induced increased metabolism of T4 was determined to be the cause of proliferative changes to the rat thyroid. The

clinical relevance of these findings is not known but rodents are more sensitive to changes in thyroid hormone metabolism than humans.

In a two year oral carcinogenicity study in mice, silodosin resulted in significantly higher incidences of mammary gland tumours (adenocarcinoma and adenoacanthoma) in females at doses ≥ 150 mg/kg/day (≥ 41 times the clinical AUC at the MRHD). In males benign testicular tumours (Leydig cell adenoma, gonadostromal tumour) were seen at doses ≥ 60 mg/kg/day (≥ 5 times the clinical AUC at the MRHD). Both mammary gland and testicular tumours are likely secondary to silodosin-induced hyperprolactinaemia, which can directly induce proliferative changes in mammary glands or induce neoplasms in reproductive tissue by altering gonadotropin release. The clinical relevance of these findings is uncertain but hyperprolactinaemia-associated tumours have been observed in rodents with other alpha adrenoceptor antagonists that have an established history of clinical use. Silodosin has not been shown to elevate prolactin levels in clinical trials.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

UROREC contains silodosin, pregelatinised maize starch, mannitol, magnesium stearate and sodium lauryl sulfate. The 4 mg hard capsule shell contains gelatin, titanium dioxide and iron oxide yellow. The 8 mg hard capsule shell contains gelatin and titanium dioxide.

6.2. Incompatibilities

Refer to *section 4.5 Interactions with Other Medicines and Other Forms of Interactions*.

6.3. Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. Special Precautions for Storage

Store UROREC below 25°C in the original package in order to protect from light and moisture.

6.5. Nature and Contents of Container

UROREC trade packs contain thirty capsules and starter packs contain ten capsules. Both trade and starter packs are provided in PVC/PVDC/aluminium foil blisters, packed in a carton.

6.6. Special Precautions for Disposal

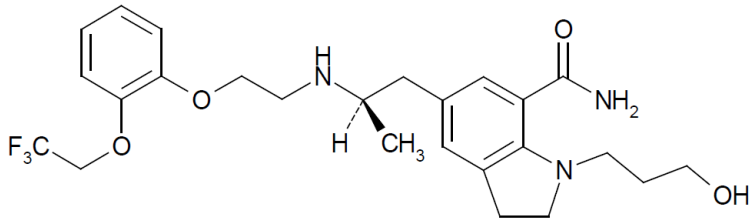
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7. Physicochemical Properties

Silodosin is a white to pale yellowish powder. It is very slightly soluble in water (0.17 mg/mL) and slightly soluble in alcohol (119 mg/mL) with a partition coefficient Log P = 2.87 (2.45 – 3.34). Silodosin present two pKa (pKa1: 8.53, N-ethylaminopropyl group and pKa2: 4.03, N-indoline ring).

Chemical Structure

The chemical structure is:



The chemical name is 1-(3-Hydroxypropyl)-5-[(2*R*)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide.

The molecular weight is 495.53.

Cas Number

The CAS registry number is 160970-54-7.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Mayne Pharma International Pty Ltd

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9. DATE OF FIRST APPROVAL

23 May 2017

10. DATE OF REVISION

27 July 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	PI reformat only