Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Silodosin

Proprietary Product Name: Urorec

Sponsor: Mayne Pharma International Pty Ltd

October 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
5-ARI	5-α-reductase inhibitors
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
Ae_{0-240}	amount excreted through 240 h post-dose
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST(GOT)	aspartate aminotransferase (glutamic oxaloacetic transaminase)
AST(GPT)	aspartate aminotransferase (glutamic pyruvic transaminase)
ATC	Anatomical Therapeutic Chemical classification system
AUA	American Urological Association
AUC	Area Under plasma Concentration time curve
AUC_{BP}	Area Under the linear-linear Curve for blood pressure
BCS	Biopharmaceutics Classification System
bd	Twice daily *(bis die)*
BMI	Body Mass Index
BP	Blood Pressure
BPH	Benign Prostatic Hyperplasia
bpm	beats per minute
BUN	(Blood) Urea Nitrogen
C2h	Predicted plasma concentration 2 h following drug administration
C12h	Predicted plasma concentration 12 h following drug administration
C_{CR} or CL_{CR}	Creatinine Clearance
CFB	Change From Baseline
CI	Confidence Interval
CL_{tot}/F	Total body clearance
C_{max},	Maximum plasma concentration

Abbreviation	Meaning
$C_{max,ss}$	Maximum plasma concentrations at steady-state
$Cmin_{ss}$	Minimum plasma concentrations at steady-state
Cre	Creatinine
CRP	C-reactive protein
CSR	Clinical Study Report
CVA	Cerebro Vascular Accident
DB	Double-Blind
DBP	Diastolic Blood Pressure
EAU	European Association of Urology
ECG	electrocardiogram
EU	Europe (European)
F	Bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOE	Failure Of Ejaculation
GCP	Good Clinical Practice
GLS	Geometric Least Squares Mean
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
h	Hour
Hb	Haemoglobin
HLS	Huntingdon Life Sciences, Ltd
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
Ht	Haematocrit
ICH	International Conference on Harmonisation
IPSS	International Prostate Symptom Score- subjective symptoms including

Abbreviation	Meaning
	nocturia, feeling of residual urine, voiding within 2 h, intermittence of urinary stream, urinary urgency, voiding with weak urinary stream, and straining on voiding
ITT	Intent-To-Treat Population
IV	Intravenous
K_e or Kel	Elimination rate constant
KMD-3213	Silodosin
KMD-3213G	Silodosin glucuronide
LC/MS/MS	HPLC combined with tandem mass spectroscopy
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOC	Loss Of Consciousness
LOCF	Last Observation Carried Forward
LUTS	Lower Urinary Tract Symptoms
MedDRA	Medical Dictionary for Regulatory Activities
MFR	Maximum Flow Rate
mITT	Modified Intent-To Treat
mmHg	Millimetres of mercury
MONO	Monocyte
ms	Millisecond
N/A	Not applicable
NAD	Nicotinamide Adenine Dinucleotide
OC	Observed Cases
OL	Open Label
OLE	Open-Label Extension (Study)
PD	Pharmacodynamics
PHI	Protected Health Information
PK	Pharmacokinetics

Abbreviation	Meaning
PopPK	Population Pharmacokinetics
PP	Per Protocol Population
PSA	Prostate Specific Antigen
PT	Preferred Term
Q_{max}	Maximum urine flow
QoL	Quality Of Life
RMS	Root-Mean-Square
SAE	Serious Adverse Event
SAF	Safety Analysis Population
SAS®	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error of the Mean
silodosin-G	Silodosin glucuronide
SOC	System Organ Class
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Events
TFT	Thyroid Function Test(S)
TG	Triglyceride
td	Drug administration three times daily
T_{max}	Time at which C_{max}, occurred
TURP	Transurethral Resection Of The Prostate
ULN	Upper Limit Of Normal Range
URTI	Upper Respiratory Tract Infection
US	Unites States
UTI	Urinary Tract Infection
Vdss/F or Vd	Volume of distribution

Abbreviation	Meaning
WBC	Caucasian Blood Cell Count
γ-GTP	Gamma-Glutamyltranspeptidase

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 May 2017
Date of entry onto ARTG	23 May 2017
Active ingredient(s):	Silodosin
Product name(s):	Urorec
Sponsor's name and address:	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106
Dose form(s):	Hard capsule (gelatine)
Strength(s):	4 mg and 8 mg
Container(s):	Blister pack
Pack size(s):	10 (starter packs) and 30 capsules
Approved therapeutic use:	*Urorec is indicated for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended dose is one capsule of Urorec 8 mg daily. For special patient populations, one capsule of Urorec 4 mg daily is recommended. For more details see Product Information (Attachment 1).
ARTG number (s):	275256 and 275265

Product background

This AusPAR describes the application by the sponsor to register a new chemical entity silodosin as Urorec for:

> *Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men*

This was revised to

> *Relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult men.*

during the TGA's evaluation of this submission.

The sponsor proposed the following dosage regimen:

> *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.*
>
> *The recommended dose is one capsule of Urorec 8 mg daily. For special patient populations, one capsule of Urorec 4 mg daily is recommended (see below).*
>
> *No dose adjustment is required in the elderly.*
>
> *No dose adjustment is required for patients with mild renal impairment (CLCR ≥ 50 to ≤ 80 ml/min). A starting dose of 4 mg once daily is recommended in patients with moderate renal impairment (CLCR ≥ 30 to <50 ml/min), which may be increased to 8 mg once daily after one week of treatment, depending on the individual patient's response. The use in patients with severe renal impairment (CLCR <30 ml/min) is not recommended.*
>
> *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.*

Silodosin is a highly selective alpha (α) 1A-adrenoreceptor blocker. α1A-adrenoreceptors are primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these α1A-adrenoreceptors causes the smooth muscle in these tissues to relax, thus decreasing bladder outlet resistance without affecting detrusor smooth muscle contractility. Urorec is similar to the previously approved α1-adrenoceptor blocking agent Flomaxtra (tamsulosin). Flomaxtra is indicated '*for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).'*

Benign prostatic hyperplasia (BPH) is a common condition affecting up to 50% of men over 50 years and more than 80% of men over 80 years. There is a gradual and progressive obstruction to urine flow and increased muscle tone and resistance within the gland. These factors lead to LUTS such as hesitancy, impaired flow, frequency, nocturia and eventually urinary retention and upper urinary tract dilatation. Up to 90% of men between 45 and 80 years of age suffer LUTS of some degree. However, prostate size and symptoms are often poorly correlated with considerable variability between subjects. The syndrome of LUTS due to BPH has significant effects on quality of life, with the symptoms described in treatment guidelines as 'bothersome'.

Besides the general guidelines, there are no specific TGA adopted European guidelines relevant to this submission, that is, for drugs used in the management of symptoms related to benign prostatic hyperplasia. Guidelines of some interest would be:

- pp. 127-132 of Rules 1998 (3C)-3CC6a Clinical Investigation of Medicinal Products for Long-Term Use

Regulatory status

The product received its initial registration on the Australian Register of Therapeutic Goods (ARTG) on the 23 May 2017.

Silodosin is approved in the US (2008), Europe (2010) and Canada (2011) for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). The following table summarises the international regulatory status (Table 1).

Table 1: International regulatory status

Country/region	Status	Indications (approved or requested)
EU centralised procedure	Approved on 29 January 2010	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men
United States of America	Approved on 08 October2008	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
Canada	Approved on 12 January 2011	Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)
Singapore	Withdrawn	
Switzerland	Approved on 09 June 2016	Symptomatic treatment of the functional disorders associated with benign prostatic hyperplasia (BPH)

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction

The sponsor has applied to register silodosin in 4 mg, and 8 mg strengths capsules marketed under the trade name 'Urorec' capsules.

The maximum daily dose of Urorec is 8 mg/day, taken with food. The PI states that food decreases maximum plasma concentration (C_{max},) by approximately 30 %, increases time to C_{max}, (T_{max}) by approximately 1 h and has little effect on the area under the plasma concentration versus time curve (AUC).

Other structurally related α1-adrenoreceptor antagonist substances include tamsulosin. Tamsulosin is registered in Australia as 400 µg prolonged release tablets, with recommended dosage of 0.4 to 1.2 mg once daily, taken with or without food.

Drug substance (active ingredient)

Silodosin is a white to pale yellowish white powder with the chemical name is (-)-1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2- trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide according to the International Union of Pure and Applied Chemistry (IUPAC) nomenclature.

Silodosin administered orally is well absorbed and absorption is dose proportional. The absolute bioavailability is approximately 32 %. 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 (standard deviation(SD)), T_{max} 2.5 h (range 1.0-3.0), AUC 433 ± 286 ng.h/mL.

Silodosin undergoes extensive metabolism through glucuronidation (UGT2B7), alcohol and aldehyde dehydrogenase and oxidative pathways, mainly cytochrome P450 (CYP) isozyme 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 ($t_{½}$ approximately 24 h) and reaches plasma concentrations approx. 4 times higher than silodosin. In vitro data indicate that silodosin does not inhibit or induce CYP pH enzyme systems.

The partition coefficient (LogPoctanol/water) of silodosin is 2.87, with dissociation constants (pKa1) of 8.53 (very slightly basic, N-ethylaminopropyl group) and (pKa2) of 4.03 (N-indoline group). Silodosin solubility decreases with increasing pH and is very slightly soluble in water. Silodosin is not considered to be hygroscopic and it is very soluble in acetic acid, freely soluble in methanol, N,N-dimethylformamide (DMF), ethanol and sparingly soluble in 1-octanol. The active substance is soluble in various buffers at acidic pH but very slightly at alkaline pH.

The polymorphic form is the α form (3 polymorphs have been reported to exist).

Silodosin contains one chiral centre and is used as the R-enantiomer.

The active ingredient is purified by recrystallisation and de-lumped. Structural characterisation was provided using appropriate methods.

The drug substance specification includes tests and limits for the stereoisomer and one identified related substance. The limits for the each unspecified impurity are in line with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) identification threshold. The active substance specifications include tests for appearance (white to pale yellowish white powder), identification, heavy metals (European Pharmacopeia (Ph.Eur.)), sulphated ash (Ph.Eur.), impurities, assay, loss on drying (Ph.Eur.) and residual solvents (Ph.Eur.). Impurities were described, classified as process-related impurities and possible degradation products, and qualified. Potential genotoxic impurities were below the qualification threshold. Residual solvents are controlled in according to ICH requirements.

The API is considered to be Biopharmaceutic Classification system (BCS) class 3 (high solubility, low permeability).

Drug product

The proposed hard capsules are distinguished by colour, and size:

- 4 mg: An opaque yellow/opaque yellow size 3 hard gelatine capsule
- 8 mg: n opaque white/opaque white size 0 hard gelatine capsule

The capsule manufacturing process uses standard processes such as mixing, wet granulation, sieving, drying, blending, encapsulation and packaging. The process has been validated and in-process controls are adequate for the dose form.

The excipients are conventional and include: mannitol, pre gelatinised maize starch, sodium lauryl sulphate and magnesium stearate. Other ingredients of the capsule shell are gelatine, titanium dioxide (both strengths) and iron oxide yellow colourant (4 mg strength only).

The hard capsules are packed in blister packs in cartons containing 10 capsules (starter packs) and 30 capsules.

The finished product specifications include tests for appearance (visual), identification, assay, impurities, uniformity of dosage units, dissolution and microbial quality. Assay limits comply with TGO 78[1]. Impurity limits have been qualified. The dissolution method was shown to be discriminatory for various formulation and manufacturing parameters.

The stability data provided supports a shelf life of 36 months when stored below 25°C (stored in the original package to protect from light and moisture).

Biopharmaceutics

During product development supplies of silodosin capsules have been made by 3 different methods of manufacture. The initial capsules were used in early clinical studies (manufacturing method A). Capsules made using methods B and C were used in Phase II and Phase III clinical studies.

The formulation proposed for marketing is identical to that used for the Phase II and Phase III clinical trials which were manufactured by applying the wet granulation process, (method C). An active and placebo Phase III efficacy study (IT-CL-0215) was conducted with the proposed 8 mg capsule. Dose finding (US021-99) and the 2 placebo studies (SI04009, SI04010) were performed with a 4 mg final marketing formulation (made using method C). Initial formulation development was performed on silodosin 2 mg and 4 mg strengths. The wet granulation process was selected (method C) and used to manufacture formulations used in Phase I, II and III studies. The 8 mg product was developed as a direct scale of the 4 mg product and uses the same manufacturing method (method C).

Comparative dissolution profiles were obtained for the 4 mg and 8 mg capsules using 3 different dissolution media pH 1.2, 4.5, 6.8. Based on the disintegration data and dissolution results provided and according to the Note of Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) the applicant justified the absence of an in vivo test to demonstrate the equivalence of the different capsules formulations. Note: the FDA agreed that based on an in vitro comparison no bioequivalence study was required to support approval of the 8 mg product. Absolute bioavailability was provided (Study KMD-308).

The method development processes were:

- Method A (capsule obtained by a dry blending manufacturing process was initially selected to avoid any potential crystalline form change via mechanical stress). These batches had issues with fill weight variance, adhesion surfaces and poor fluidity due to cohesion.
- Method B (granulation process using a corn starch paste). These batches also had cohesion issues.

[1] Therapeutic Goods Order No. 78. Standard for Tablets and Capsules

- Method C (proposed wet-granulation manufacturing process); formulation 4C is the same as the proposed product formulation.

There were nine clinical studies consisting of three pivotal Phase III efficacy studies; a single Phase II efficacy study; three open-label, long-term extension studies (EU and US); and two efficacy and safety studies in Japanese patients.

The key biopharmaceutic studies provided findings are summarised below.

Absolute bioavailability Study KMD-308

The absolute bioavailability of silodosin was investigated in an open-label cross-over study after a single dose of 4 mg compared to a single 2 mg intravenous (IV) administration over 4 h (KMD-308). The study also assessed the food effect after single oral doses of 4 mg. The study title in the report is 'Examination of Food Effect in Single Oral Administration and Pharmacokinetics in Single Intravenous Administration'. The 4 mg batch assessed in this study was batch XI06B, manufactured at Kissei Pharmaceutical Col., Ltd (not proposed finished product manufacturing site), made using method C. The study examined the effect of food and pharmacokinetics comparing the intravenous and oral administration routes in 12 healthy Japanese subjects.

In Phases I and II of this study a single oral dose of a 4 mg capsule of silodosin was administered under fasting/non-fasting (30 min after eating) with 150 mL of water. In Phase III a single IV dose of 2mg of silodosin was administered under fasting conditions at an infusion rate of 60 mL/h for 4 h (2 mg/240 mL of IV solution was prepared with injectable physiologic saline). The interval between doses was 7 days. One subject dropped out of the study during Period I and was excluded from the PK analyses in Periods II and III. PK analysis was performed for the remaining participants (6 in group A and 5 in group B).

The mean (±SD) C_{max},, $AUC_{0\text{-}48h}$ T_{max} and $t_{1/2}$ values for silodosin following administration of a single, 4 mg oral dose under fasted conditions were 27.986 ± 9.555 ng/mL, 135.853 ± 55.370 ng.h/mL, 1.36 ± 1.12 h and 4.714 ± 3.710 h, respectively, whereas, under fed conditions, the C_{max}, was 22.975 ± 10.841 ng/mL, $AUC_{0\text{-}48h}$ was 128.823 ± 64.127 ng.h/mL, T_{max} was 2.09 ± 0.74 h and $t_{1/2}$ was 5.981 ± 4.785 h.

Following a single 2 mg IV dose of silodosin under fasted conditions the C_{max}, was 42.91 ± 7.90 ng/mL, $AUC_{0\text{-}4h}$ was 210.01 ± 40.458 ng.h/mL, T_{max} was 4.00 ± 0.00 h and $t_{1/2}$ was 3.61 ± 1.72 h.

Food effects were considered by the clinical evaluator. The RMS ratio (90%CI) of fasting with respect to non-fasting following a single 4 mg oral administration was 130.38 (102.54, 165.78) for silodosin C_{max}, and 106.74 (87.30, 130.51) for $AUC_{0\text{-}48h}$.

The mean (±SD) bioavailability (F) following a 4 mg oral administration under fasted conditions with respect to a 2 mg IV administration was 32.238 ± 11.347%. The meal given in the Study KMD-308 was moderate fat-moderate calories. The study design, conduct and analysis were considered to be satisfactory.

The study showed a difference between under non-fasting and fasting conditions. The study considered that absorption sped up because the transition to the small intestine, the principal organ of absorption, took place rapidly under fasting than non-fasting, $AUC_{0\text{-}48h}$, an indicator of the amount of absorption, suggested that there was no difference between under non-fasting and under fasting. While C_{max}, of silodosin unaltered substance increased by about 30% under fasting as compared with non-fasting. Mean plasma curves for silodosin and for the glucuronide metabolite were included.

Absorption Study SI07004.

This study examined the dose proportionality of silodosin following treatment with either a single oral dose of 4 mg (1 x 4 mg capsule) or 8 mg (2 x 4 mg) silodosin in 22 healthy males following breakfast using 4 mg capsules formulated according to the proposed method for marketing. The mean C_{max},, AUC_{0-24}, T_{max} and $t_{1/2}$ values were 54.5 ng/mL, 290.6 ng.h/mL, 2.4 h and 13.3 h, respectively following a single oral 8 mg dose of silodosin (2 x 4 mg capsules), formulated according to the proposed method for marketing batches, to 22, healthy and predominantly Caucasian males. For the 4 mg, oral dose the values were 28.7 ng/mL, 144.7 ng.h/mL, 2.3 h and 11.1 h, respectively.

Studies 95283, 98363, UK01-97, UK02-97 and 98364, examined dose-proportionality following single oral doses ranging 0.1 to 16 mg; using batches of silodosin formulated using Method A.

Bioavailability during multiple dosing

Four PK studies examined the PKs of silodosin following multiple doses of silodosin formulated according to Method C:

- Study SI07004, examined the dose-proportionality of silodosin and metabolites silodosin-G and KMD-3293 in healthy males following seven daily doses of 4 mg (1 x 4 mg) or 8 mg (2 x 4 mg capsules). The results indicated that silodosin C_{max}, and AUC were dose-proportional following seven daily doses, whereas, there was little difference between the T_{max}, $t_{1/2}$ and Kel values following doses of either strength. For instance, following multiple 8 mg doses, the mean C_{max},, AUC_{0-24}, T_{max}, $t_{1/2}$ and Kel values for silodosin were 51.1 ng/mL, 297.3 ng.h/mL, 2.5 h, 14.4 h and 0.055/h, respectively, whereas, following the 4 mg dose the values were 28.4 ng/mL, 159.5 ng.h/mL, 2.4 h, 15.3 h and 0.055/h, respectively.
- Study SI06004 also examined the PKs of silodosin following administration of silodosin 8 mg once daily for 7 days. On the whole, the C_{max}, AUC_{0-24} and T_{max} values in this study were similar to those seen in preceding study (61.6 ng/mL, 373.4 ng.h/mL and 2.6 h, respectively).
- The QT study SI05014 examined the PKs of silodosin following 5 days of treatment with either 8 mg or 24 mg. Once again following multiple doses of 8 mg silodosin the values of the PKs parameters were similar to those seen in other studies using formulation C. For example, in this study the C_{max},, AUC, T_{max} and $t_{1/2}$ values for silodosin were 42.5 ng/mL, 299.3 ng.h/mL, 2.3 h and 7.6 h, respectively. Following 5 days of dosing with 24 mg/day the corresponding PK values were 143.9 ng/mL, 899.2 ng.h/mL, 2.4 h and 6.6 h, respectively.
- Study SI05008 examined multiple doses of formulation C ranging from 16 mg to 64 mg per day for 3 days. Although no formal PK analysis was undertaken in regards to the results of this study, the authors indicate that silodosin appeared to demonstrate linear kinetics over the dose range of 16 to 48 mg.

One study, UK02-97 examined the PKs of silodosin formulation A following 5 days of dosing with a range of dose strengths (0.1 mg, 1.0 mg and 4 mg) in 36 Caucasian males. In this study, accumulation in AUC_{0-24h} at Day 5 compared to Day 1 values was relatively low with accumulation ratios of 1.3 and 1.2 fold following doses of 0.1 and 1.0 mg, respectively

Administration timing effect

Two studies (98364 and 95284) examined the PKs of silodosin following multiple-daily doses of formulation A in healthy Japanese males.

- In Study 98364, subjects were orally administered repeat doses of 4, 6 or 8 mg of silodosin twice daily (bd) for 7 days except for once daily on Days 1 and 7 (a total of 12 doses). Analyses of Variance (ANOVAs) were conducted to compare silodosin PKs on Days 1 and 7. For the 4 mg dose the mean differences in silodosin $AUC_{0\text{-}24h}$, C_{max}, and $t_{1/2}$ values between Day 1 and Day 7 were not statistically significant with values of -13.54%, 6.976% and 50.36%, respectively. Similarly for the 6 mg and the 8 mg twice daily (bid) doses, the mean differences between Day 1 and Day 7 in $AUC_{0\text{-}24h}$, C_{max}, and $t_{1/2}$ were also not statistically significant and differences ranged between -15.52% to -22.23%, -21.63% to 11.28% and -2.924% and 50.92% for the 3 PK parameters, respectively. Simulation of silodosin PKs following repeated doses of 4 mg, 6 mg and 8 mg bid revealed that the plasma concentrations of silodosin reached steady-state on Day 3 of treatment with $C_{max,ss}$ values of 32.1412, 42.1492 and 70.8592 ng/mL, respectively, $C_{min,ss}$ values of 3.56196, 3.67408 and 6.85041 ng/mL, respectively and accumulation rates of 1.11612, 1.09949 and 1.136618 times, respectively.
- Study 95284 examined the PKs following administration of 1.5 mg silodosin three times (tid) a day for 7 days. As in the preceding study steady-state was reached on Day 3 with a $C_{max,ss}$ of 12.63 ± 5.81 ng/mL and C_{minss} of 0.90 ± 0.60 ng/mL. The accumulation ratio from the first administration was 1.29 fold. The mean differences in $AUC_{0\text{-}24}$, C_{max}, and $t_{1/2}$ between Day 1 and Day 7 were 17.03%, 20.52% and 61.86%, respectively, but none of the differences in values were identified as being clinically significant.

Volume of distribution

- Study KMD-309, examined the volume of distribution (Vdss/F) of silodosin in healthy subjects using formulation C. The objective of this study was to compare the PKs and safety of a single oral dose of silodosin in subjects with impaired renal function with those in subjects with normal renal function. Following a single, oral, 4 mg dose in fasted healthy subjects, the Vdss/F was 263.947L.
- Two other studies, UK01-97 and 98363, examined the V/d following a 4 mg dose of silodosin formulated according to method A. In these studies the V/d values were 203 L and 189.14 L, respectively.

Plasma protein binding, erythrocyte distribution and tissue distribution

- Plasma protein binding was examined in a number of in vitro studies that utilised human biomaterials including Studies PK10153, DMPK2003-0053, DMPK2004-0033 and PK10091. The results indicated that the binding rate against human plasma protein was almost constant regardless of the concentration of radioactively labelled ([^{14}C]) silodosin added, and was between 94.6% and 95.8%. The binding rates of [^{14}C]-silodosin for albumin, α1-acid glycoprotein and γ–globulin ranged from 34.7% to 35.4%, 94.3% to 96.0%, and 4.6% to 7.4%, respectively; suggesting that silodosin is predominantly bound to α1-acid glycoprotein. The blood cell transfer ratio determined from the radioactivity concentration in blood and plasma after addition of [^{14}C]-silodosin to human blood was 2.2% to 3.7%, suggesting that only a small percentage of silodosin is bound to erythrocytes. Given the volume of distribution (263.9 L) it can be assumed that silodosin is highly distributed to the tissues.

Other studies included assessment of renal clearance, metabolites, hepatic impairment, renal impairment, age and interaction with medications including diltiazem, digoxin and ketoconazole.

The clinical evaluator concluded:

- It is proposed that single capsule of either 8 mg or 4 mg silodosin will be taken with food at the same time every day.
- Following administration of a 4 mg dose of the proposed formulation to healthy Japanese subjects, the RMS ratio (90%CI) of fasting with respect to non-fasting was 130.38 (102.54, 165.78) for silodosin C_{max}, and 106.74 (87.30, 130.51) for $AUC_{0\text{-}48h}$.
- Following a single, 8 mg dose, oral of silodosin to healthy males the mean C_{max}, $AUC_{0\text{-}24h}$, T_{max} and $t_{1/2}$ values were 54.5 ng/mL, 290.6 ng.h/mL, 2.4 h and 13.3 h, respectively. For the 4 mg, oral dose the values were 28.7 ng/mL, 144.7 ng.h/mL, 2.3 h and 11.1 h, respectively.
- The mean ± SD bioavailability following a 4 mg oral administration under fasted conditions with respect to a 2 mg IV administration was 32.238 ± 11.347%.
- The C_{max} and $AUC_{0\text{-}24h}$ of silodosin increased proportionally with dose from 4 mg to 8 mg. For instance, following a 4 mg dose the C_{max}, and $AUC_{0\text{-}24h}$ values for silodosin were 28.7 ng/mL and 144.7 ng.h/mL, respectively, whereas, following an 8 mg dose the values were 54.5 ng/mL and 290.6 ng.h/mL, respectively.
- Following seven daily doses of 4 mg (1 x 4 mg) or 8 mg (2 x 4 mg capsules) silodosin the C_{max}, and AUC were dose-proportional, whereas, there was little difference between the T_{max}, $t_{1/2}$ and Kel values following doses of either strength.
- In subjects administered repeated doses of 4, 6 or 8 mg of silodosin bd, ANOVA analysis indicated that there was no significant difference in silodosin $AUC_{0\text{-}24h}$, C_{max} or $t_{1/2}$ values following 1 and 7 days of dosing.
- Steady-state appeared to be achieved following 3 days of dosing with silodosin.
- Following a single, oral, 4 mg dose in fasted healthy subjects the Vdss/F was 263.947 L. Human plasma protein binding was almost constant regardless of the concentration of [^{14}C]-silodosin added, ranging between 94.6 and 95.8%. Silodosin is predominantly bound to α1-acid glycoprotein. Only a small percentage (2.2% – 3.7%) of silodosin is bound to erythrocytes. Given the volume of distribution (263.947 L) it can be assumed that silodosin is highly distributed to the tissues.
- In humans silodosin is converted to at least five primary metabolites: KMD-3293, silodosin-G, KMD-3289, KMD-3310 and KMD-3241 and 2 secondary metabolites: KMD-3241-G and KMD-3295. In vitro studies indicated that silodosin was primarily metabolised by CYP3A4 and two other CYP species, CYP1A1/2 and 2D6, may be involved. Formation of the metabolite KMD-3310 primarily occurred via CYP3A4 mediated metabolism of silodosin. By contrast, CYP plays almost no role in the generation of KMD-3293, whereas, nicotinamide adenine dinucleotide (NAD) is necessary as a coenzyme and both alcohol dehydrogenase and aldehyde dehydrogenase are assumed to be involved in generation of KMD-3293.
- The main route of excretion of [^{14}C]-silodosin-derived radioactivity following oral dosing was via the faeces, with a mean of 54.9% excreted via this route through 240 h post-dose.
- Of the two main metabolites, only the functional activity of silodosin-G for the α1A-adrenergic receptors has been determined. It has been estimated that the effect of silodosin-G may account for 16% to 28% of the total activity at α1A-adrenergic receptors.
- Following 7 days dosing with 8 mg silodosin the C_{max}, and $AUC_{0\text{-}24h}$ values for silodosin were 61.6 ng/mL and 373.4 ng.h/mL, respectively, whereas, for the metabolites silodosin-G they were 102.4 ng/mL and 1661 ng.h/mL, respectively; for KMD-3293 they were 34.3 ng/mL and 373.0 ng.h/mL, respectively; for KMD-3295 they were 3.4

ng/mL and 16.8 ng.h/mL, respectively; and for KMD-3310 they were 1.6 ng/mL and 2.8 ng.h/mL, respectively.

- The mean 0 to 240 h recovery of radioactivity in excreta, including faecal wipes, and urine was 88.4%. Following an oral dose of [^{14}C]-silodosin, radioactivity excreted in urine consisted primarily of three major metabolites and parent drug. Silodosin, KMD-3293, KMD-3310 and M-4 accounted for 10.7%, 10.8% 19.9% and 18.9%, respectively, of the urinary radioactivity and 3.6%, 3.6%, 6.5% and 6.5%, respectively, of the dose radioactivity.
- [^{14}C]-silodosin radioactivity excreted in faeces consisted primarily of KMD-3293 and silodosin with metabolite and parent accounting for 36.9% and 28.0%, respectively, of the faecal radioactivity and 20.5% and 15.4%, respectively, of the dose radioactivity. Excretion in the urine accounted for a mean of 33.5% of the administered radioactivity through 240 h post-dose.

Intra and inter individual variability of PKs

- The %CV values associated with $AUC_{0\text{-}24h}$ following a single dose of either 4 mg or 8 mg silodosin were 45.4% and 36.3%. For C_{max}, these values were 46.1% and 47.6%.
- PopPK analysis estimated that the mean variation on CL and Vd in the target population was 0.049 and 0.032, respectively. The residual sum of the squares was 0.233.

Pharmacokinetics in the target population

- In patients with BPH there was no silodosin accumulation following multiple-doses. In the target population the estimated mean CL and Vd were 0.302 L/h/kg and 2.24 L/kg, respectively.

Pharmacokinetics in special populations

- Following a single 8 mg dose, silodosin C_{max}, and $AUC_{0\text{-}inf}$ values for total concentrations (bound + unbound) were lower (approximately 20%) in subjects with liver dysfunction compared to healthy controls, whereas, the C_{max}, and AUC values for unbound concentrations were 10 to 20% higher. The bound and unbound ratios for silodosin-G $AUC_{0\text{-}inf}$ were 0.8 and 0.5, respectively, and for KMD-3293 were 0.6 and 0.8, respectively.
- Silodosin AUC_{tlast} increased by approximately1.7 and 2.0 fold respectively for the unbound and total silodosin in patients with mild to moderate renal impairment compared to a control group. A similar increase of about 2 fold was observed for AUC_{tlast} of total silodosin in the patients with severe impairment; whereas an approximately3.7 fold increase in unbound silodosin was observed.
- In subjects with moderate to severe renal impairment the GLS mean for C_{max} and $AUC_{inf\ [total\ concentration]}$ of unchanged silodosin was 3.11 and 3.22, respectively, compared to healthy subjects. For unbound concentration the ratios for silodosin C_{max} and AUC_{inf} values were 1.49 to 2.01, respectively.
- There appeared to be no age-related effects on the PKs of silodosin in healthy elderly and non-elderly subjects.

Population PK

- PopPK analysis undertaken using the PK data from 258 target patients who underwent long-term treatment with silodosin identified body weight, age, creatinine, ALT and CRP as significantly influential covariates on either silodosin CL or Vd.

Drug-drug interactions

- Administration of a single oral dose of 300mg of the prolonged-release CYP3A4 inhibitor diltiazem with a single 8 mg dose of silodosin had little effect on silodosin C_{max},; however, silodosin AUC_{inf} increased by 32% and median T_{max} was delayed by 1.25 h. Similarly, the AUC_{inf} of KMD-3293 and silodosin-G were increased by 28% and 37%, respectively, in the presence of diltiazem.
- Steady-state plasma concentrations of silodosin had no effect on the steady-state PKs of the P-glycoprotein substrate digoxin.
- Following co-administration of multiple oral doses of 400 mg ketoconazole, a potent CYP3A4 inhibitor, and a single dose of 8 mg silodosin, the AUC_{inf} for silodosin, silodosin-G and KMD-3293 increased 3.1-, 3.0- and 2.5-fold, respectively, whereas, C_{max}, values increased 3.7, 3.2 and 2.8 fold, respectively.

In vitro interactions

- Silodosin is a weak inhibitor of CYP3A4, CYP2D6, CYP2B6 and CYP2C8. Out of a range of CYP3A4 inhibitors, only nifedipine and ketoconazole inhibited the metabolism of silodosin with IC50 values of less than 25 μM. There is little evidence that silodosin induces CYP1A2, CYP3A4/5, CYP2C8, CYP2C9, CYP2C19 or CYP2B6. P-gp appears to be involved in the directional transport of silodosin.

Quality summary and conclusions

There following are outstanding issues with the chemistry and quality control aspects of the products.

- GMP clearances will need to be provided prior to registration.

Registration is otherwise recommended with respect to chemistry and quality perspective.

III. Nonclinical findings

Introduction

General comments

The overall quality of the nonclinical dossier was satisfactory and in general accord with the ICH guideline for the nonclinical assessment of pharmaceuticals[2]. However, (and perhaps reflecting the age of the studies) not all the pivotal toxicity studies were conducted according to GLP. Nevertheless, the design and scope of the nonclinical testing strategy employed was appropriate and where necessary additional studies were conducted to further elucidate and characterise possible mechanisms behind treatment-

[2]ICH M3 Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

related changes. The sponsor also provided studies to toxicologically qualify a major metabolite unique to humans; glucuronidated silodosin (KMD-3213G).

Silodosin is a chiral substance, existing as the R-enantiomer. No studies were conducted to assess possible pharmacological activity of the S-silodosin. However concerns about unintended activity by contaminating levels of the S-silodosin are somewhat allayed by investigations that demonstrated minimal in vivo racemic conversion. In response to a question on whether they could provide supporting material to toxicologically qualify the S-isomer, the sponsor referred to toxicity studies as supporting material. Based on the sponsor's rationale and dose multiples attained in the animal studies the proposed limit is considered acceptable.

As an α1-adrenergic receptor antagonist, silodosin belongs to the same pharmacological class as tamsulosin, terazosin, prazosin and alfuzosin which are all registered for use in Australia and indicated for the treatment of BPH.

Duration of use of Urorec was not specified but is likely to be chronic in responding patients.

Pharmacology

Primary pharmacology

Silodosin is an α1-adrenergic receptor (AR) antagonist that has been developed to preferentially target the α1A AR subtype that is expressed by prostatic tissue and underlies many of the urinary symptoms associated with BPH.

Radioligand binding studies were conducted to confirm binding affinity and selectivity of silodosin for its intended receptor target, α1A AR. Silodosin exhibited nanomolar affinity for the α1A AR using either rodent tissue (rat submandibular gland α1A AR Ki 0.12 nM) or cell expression systems (recombinant human α1A AR pKi 10.4±0.1) as the source of target protein (receptors). Other α1 AR antagonists prazosin and tamsulosin had similar affinity for α1A AR (pKi of 9.91 and 10.9, respectively); however they also had similarly high affinities for subtypes α1B (pKi of 10.6 and 9.92, respectively) and α1D (pKi of 10.1 and 10.5, respectively), whereas silodosin exhibited lower affinities for these receptor subtypes (pKi for α1B: 8.19 and α1D:8.66; 161 and 55 times lower than for α1A). A major human metabolite of silodosin, MD127, did not exhibit significant affinity for any of the α1 AR subtypes; with affinities for α1A, α1B and α1D AR subtypes being 6.3, 47 and 35 times lower than silodosin, respectively. Studies on receptor affinity and functional activities on the S-enantiomer of silodosin were not conducted.

Functional demonstration of the α1 antagonist effects of silodosin was provided in isolated tissue studies, where silodosin inhibited noradrenaline-mediated contractions in isolated prostate (rat pKb: 10.15; rabbit pKb: 9.6) and rabbit urethra and bladder trigone (pKb: 8.71 and 9.35, respectively). Comparisons with other α1 antagonists, tamsulosin and prazosin, found that the activity of silodosin was closest to that of tamsulosin, while prazosin was lower (between 5.6 and 49 fold lower efficacy than silodosin). Major metabolite KMD-3213G also exhibited pharmacological activity, inhibiting rat prostatic smooth muscle contractions at levels slightly lower than parent silodosin (pKb: 9.86 compared to 10.15).

Antagonist activity was demonstrated by silodosin as well as tamsulosin and prazosin, in rat aorta and spleen, and is considered to be mediated by activity on α1D and α1B AR, respectively. Potency was lowest with silodosin in both aorta and spleen (pA2: 7.88 and 7.15, respectively) compared to tamsulosin and prazosin, and provides functional evidence to support the premise that silodosin preferentially binds to the α1A AR subtype. In vivo investigations were conducted in a rat model of BPH, where intravenous silodosin

and tamsulosin both attenuated phenylephrine induced increases in intraurethral pressure and overactive bladder like contractions to a similar extent. In another study, oral silodosin and tamsulosin dose-dependently attenuated increases in intraurethral pressure, with effects found to persist longer with high dose silodosin than tamsulosin. No further examination or comment on the extent of duration of silodosin binding and its inhibitory effects was provided, thus the reversibility of silodosin actions is uncertain. All α1 antagonists dose dependently attenuated the phenylephrine mediated increases in blood pressure and intraurethral pressure in rats. Silodosin showed greater preferential efficacy for the intraurethral effects than the other antagonists (order of efficacy: silodosin > tamsulosin > prazosin > terazosin). Similar findings were also reported in dogs where intravenous (IV) silodosin attenuated nerve-stimulated increases in intraurethral pressure to a greater extent than tamsulosin.

Overall, the primary pharmacology data provide sufficient evidence of its proposed mechanism of action to support the use of silodosin in the treatment of BPH.

Secondary pharmacodynamics and safety pharmacology

Possible off target effects of silodosin were assessed in a number of in vitro binding studies using receptor screen panels. Moderate affinity for β2 receptors was noted (Ki 5.67 nM) and was the basis for a bioassay study using isolated pregnant rat uterus. Binding to the serotonin receptor subtypes 5-HT1A, 1B, 1D and 7 receptors was also noted, with significant binding seen with the 5-HT1A subtype (Ki 0.31 nM). Furthermore, modest binding to dopamine D3 receptors (Ki 350 nM) was also demonstrated. While the bioassay study on potential β2 activity in rat uterus did not reveal any significant agonist or antagonist activity by silodosin, possible functional effects of 5-HT1A actions were not discussed or examined.

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory organ systems and were all conducted according to GLP.

In the CNS study there were incidences of tremors, reduced mobility and arousal as well as decreases in body temperatures in the high dose (HD) group (20 mg/kg). Treatment-related changes to respiratory parameters were minimal with modest increases in respiratory rates seen in the HD group but with no other changes to other parameters these effects are not considered clinically significant. In vitro studies on cardiovascular systems identified concentration dependent inhibition of potassium (hERG tail) currents by silodosin (50% inhibitory concentration (IC50) 8.91 μM) and increases in action potential duration (as APDs at 50% and 90% repolarization (APD50, APD90)) in isolated guinea pig papillary muscles. In vivo studies in conscious dogs, using doses up to 20 mg/kg, PO or 3 mg/kg IV, did not find evidence of effects on electrocardiogram (ECG) parameters.

Two non-pivotal repeat dose toxicity studies in dogs showed significantly prolonged P-waves, QRS complex and QT intervals at 400 mg/kg PO, and increased QT intervals at 200 and 500 mg/kg PO. Plasma levels achieved at 400 mg/kg (as C_{max},) were at least 270 times greater than the human C_{max}, at the maximum recommended human dose (MRHD) (silodosin 8 mg/day achieved a C_{max}, of 73.4 ng/mL after a 7 day dosing period). When factoring plasma protein binding, dog exposures were > 1000 fold greater than human C_{max}, [Dog (81% bound): 3750 ng/mL cf. Human (95% bound): 3.67 ng/mL]. Overall, because effects on QT intervals in dogs occurred at substantially higher exposures than those expected clinically, silodosin is not anticipated to be arrhythmogenic under clinical use conditions.

Pharmacokinetics

Single dose studies indicated rapid absorption of silodosin in rats and dogs (T_{max} approximately 0.1 to 1.7 h), while in humans the absorption was slower (T_{max} 1.4 to 2.3 h). Absorption was dose-proportional in rats and healthy male subjects. Plasma half-lives between animal species and subjects diverged, with shorter plasma half-lives noted in both rats and dogs ($t_{½}$ approximately 1.5 to 3.3 h) than in human subjects ($t_{½}$ approximately 8-15 h). Low oral bioavailability was reported in rats and dogs (approximately 10% and 25%, respectively). A rat study showed a prolongation of the plasma half-life in the fed state compared to fasted state, as well as a reduction in plasma exposures in the fed state compared to fasted (C_{max},: 86.9 ng/mL versus 13.1 ng/mL, respectively).

Silodosin protein binding was higher in human plasma than rat or dog plasma (approximately 95% compared to approximately 80% and 82% in each species, respectively). Silodosin metabolites KMD-3293 and KMD-3213G also showed high affinity for human plasma proteins (92%). Of the likely plasma protein targets, silodosin exhibited the highest binding with α1 acid glycoprotein (96%), while binding to albumin was approximately 35% and γ-globulin was approximately 5% to 7%.

Affinity for red blood cells ((RBCs) relative to plasma) was moderate in rats (approximately 50% associated with RBCs) while in dog and human red blood cells it was considerably lower (approximately 3% associated with RBCs). Silodosin exhibited extensive tissue distribution across most tissue types in rats. Levels of radioactivity were lowest in the CNS (cerebrum, cerebellum and spinal cord) and testis. Nevertheless, elimination half-life was long in some tissues (skin: 13 days, fat: 17 days, brown fat: 18 days, testis: 25 days). Distribution of silodosin and KMD-3213G was also monitored in rat prostate where silodosin levels were greater in the prostate than plasma at 1 and 4 h of continuous intravenous infusion but levels of KMD-3213G were considerably lower in the prostate than plasma.

Silodosin is oxidised by CYP3A4 and undergoes glucuronidation reactions by UGT 2B7. A role for alcohol and aldehyde dehydrogenases was also identified. CYP 3A4 mediated reactions generate metabolites KMD-3241, KMD-3289 and KMD-3310, which are common to rats, dogs and humans. Glucuronidation by UGT 2B7 generates the metabolites KMD-3213G and KMD-3241G which are largely unique to humans. The dehydrogenases are associated with the formation of metabolites KMD-3293 and KMD-3295, which are common to rats, dogs and humans, with KMD–3293 being a major plasma, urinary and faecal metabolite in humans. In vitro studies with human (and monkey) hepatocytes indicated extensive metabolic transformation of silodosin, with very little unchanged drug detected compared to rat and dog hepatocytes. In contrast, under in vivo conditions unchanged silodosin was a significant fraction of the radioactive dose recovered in faeces in human subjects while KMD-3213G was undetectable. A plausible reason as postulated by the sponsor is that KMD-3213G is deconjugated by enteric enzymes in the lower gastrointestinal (GI) tract and excreted as free silodosin.

Mass balance studies showed similarities in the dominant route of excretion for rats, dogs and humans. Silodosin related radioactivity was excreted predominantly through the faecal route, with studies on bile cannulated rats indicating a role for biliary excretion. The relative contribution of excretory routes for all species was approximately 55% to 87% through faecal route compared to approximately 11% to 34% through urinary excretion.

In summary, absorption of silodosin was dose proportional in all species but maximal absorption and plasma half-lives were slower in humans than in rats and dogs. High plasma protein binding was noted in humans (approximately 95% compared to approximately 80% in rats and dogs). Tissue distribution was generally extensive, though distribution was lowest in the CNS. Oxidative biotransformation of silodosin (by CYP 3A4

in humans) was common to all species; however glucuronidation was unique to humans. Predominant route of excretion for all species is the faecal route, likely involving biliary excretion. Overall, there are a number of qualitative differences in the pharmacokinetic profile of silodosin in humans compared to the test species used in nonclinical studies. Provided that appropriate toxicological qualification of the unique human metabolite is provided, these differences are not considered to be toxicologically limiting.

Pharmacokinetic drug interactions

Silodosin exhibited weak inhibitory activity against CYP2D6 and CYP3A4 (IC50: 21.7 μM and 100.3 μM). Silodosin metabolites KMD-3213G and KMD-3293 did not exhibit any significant inhibitory activity against any of the CYPs. Neither silodosin nor its metabolites exhibited CYP isozyme induction potential. Silodosin was identified as a P-gp substrate; however, potential P-gp inhibitory effects by silodosin or its metabolites were not assessed. No specific interaction potential was identified for silodosin but in view of its reliance on CYP3A4 mediated oxidation caution may be advised when co-administering silodosin with strong CYP3A4 inhibitors.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in rats and dogs where both the clinical (PO) and IV routes were used. Mortalities were seen in both species and routes. Deaths occurred within two days of administration and were preceded by dyspnea, shivering, decreased locomotor activity and tremors. Other clinical signs such as lacrimation, ptosis and increased salivation, also occurred in other pharmacology and toxicity studies and were considered pharmacologically mediated. Necropsy examinations found petechiae in the stomachs of some rats that received ≥ 1000 mg/kg and evidence of erosion, ulceration and haemorrhagic foci in the gastric mucosa of one decedent dog. Lesions were also noted in the livers of rats dosed at 800 and 1600 mg/kg. These adverse findings were seen at considerably higher doses than those used in the repeat dose studies. In surviving animals, complete recovery occurred within several days after dosing.

Overall, findings from acute exposure studies indicate that silodosin has a moderate order of acute toxicity in rats and dogs.

Repeat-dose toxicity

Repeat dose toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 52 weeks in dogs were conducted which predominantly used the oral route. As well, the sponsor submitted 2 week rat and dog studies that utilised the IV route. Durations of studies were acceptable in view of an anticipated long-term pattern of use to for providing symptomatic relief. Design aspects of the studies (types of species used, group sizes, determined parameters) were appropriate and consistent with guidelines relevant to toxicity testing.[3]

Relative exposure

Exposure ratios are calculated based on animal: human plasma $AUC_{0\text{-}24h}$ values. The animal AUC data shown is the mean of male and female values unless otherwise indicated. Human reference values are from clinical Study KMD3213-US011-98 where healthy human subjects (Mean age: 59.6±7.9) received the proposed clinical dose (8 mg/day) for 7 days.

[3] ICH M3(R2) Step 5, CPMP/SWP/1042/99 Rev 1 Guideline on repeated dose toxicity.

Table 2: Relative exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration [Study no.]	Dose (mg/kg/day)	AUC_{0-24h}^ (ng·h/mL)	Exposure ratio#
Mouse (CD-1)	13 weeks ^Prelim carcinogenicity	200	15044	38
		400	29288	74
		800	41139	104
	2 years ^Carcinogenicity Males (in Week 26)	20	299	0.6
		60	1897	4.8
		200	22810	58
	2 years ^Carcinogenicity Females (in Week 26)	60	2543	6.4
		150	16298	41
		400	64058	162
Rat (SD)	4 weeks# Toxicity Male/Female	20	701/532	1.8/1.3
		60	2568/1858	6.5/4.7
		200	11151/4106	28/10
		600	24241/7519	61/19
	13 weeks ^Preliminary Carcinogenicity	30	1798	4.5
		125	5692	14
		500	19923	50
	2 years ^Carcinogenicity Male/Female (in Week 26)	15	422/261	1.1/0.7
		50/80	2011/2235	5.1/5.6
		150/250	9509/8282	24/21
Dog (Beagle)	13 weeks Toxicity	10	3207	8
		50	27862	70
		200 (100)	39151	99
	52 weeks Toxicity (on Week 26)	5	1412	3.6
		10	7966	20
		80	29831	75
Human (healthy male subjects)	Steady state	8 mg/day for 7 days	396	–

= animal: human plasma AUC_{0-24h};; ^Based on studies that administered silodosin through the diet;
#$AUC values as AUC_{0-4h};

Major toxicities

Silodosin was associated with a number of treatment-related findings regularly seen in repeat dose studies. Target tissues included the liver, the gastrointestinal tract, the thyroid, mammary glands in female rats and male reproductive tissue. As well there was a collection of clinical changes that were consistently seen in all treated animals that reflected pharmacologically mediated activity.

Liver

Liver changes were noted in mice, rats and dogs. Changes were predominantly seen with the oral route, although there treatment related increases in liver weights were also noted in IV treated dogs. These changes included increases in liver weights, relative to body weight. Further exploration of this increase in rats was found to be associated with higher P450 microsomal content and activity. Notably, pharmacokinetic studies did not identify CYP enzyme inducing potential in silodosin. Gross findings showed higher incidences of swelling and yellow deposits on livers of animals from high dose groups. The yellowish appearance was attributed to a higher incidence of moderate to severe fatty degeneration of hepatocytes in HD treated rats, with lipid droplets of hepatocytic origin noted during microscopic assessment of tissues of rats. In dogs, the liver (as well as the gall bladder and pancreas, salivary glands) had a darkened colour due to increased deposits of a yellow brown pigment. The pigment was identified as a lipid-soluble lipofuscin-like substance. Other hepatic histological changes noted were congestion, vacuolation of centrilobular hepatocytes, dilated sinusoids and bile duct hyperplasia. Fatty associated degeneration and mild instances of focal fibrosis and/or necrosis of hepatocytes were also reported. In dogs these changes were seen at high doses (≥ 80 mg/kg/day, PO; >75 times the clinical AUC), while in rats such changes were often seen at all tested doses (from ≥ 60 mg/kg/day, PO; approximately 6 times the clinical AUC). Serum chemistry assessments revealed treatment-related reductions to triglycerides in rats and dogs and occasional increase in HDL levels in rats. In the non-pivotal studies where higher doses were tested, there were occasions of significantly higher levels of liver transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and also alkaline phosphatase (ALP).

Systemic inhibition of α1 AR by inhibitors such as doxazosin and prazosin reduces hepatic lipid metabolism, which will lower triglyceride and cholesterol levels and increase HDL cholesterol levels.[4] Therefore, reduced mobilisation of hepatic triglycerides and fatty acids is a plausible reason for liver changes seen in silodosin-treated animals. It is noted that hepatobiliary disorders are identified as anticipated adverse reactions in the approved US PI/label based on postmarketing experiences.

Gastrointestinal tract

A number of adverse histological findings in gastrointestinal tissue were noted with silodosin dosing, including in some single dose studies. In single dose studies, tissue findings also corresponded to mortalities. Petechiae were noted in the stomachs of 3 rats dosed up to 2000 mg/kg, PO and found dead within 2 days of dosing. Gross examination of a dog found dead on Day 2 after a single dose of 1500 mg/kg, PO, found evidence of erosion, ulceration and haemorrhagic foci in the gastric mucosal surface, as well as the mucosa of the duodenum and upper jejunum. In repeat dose studies, minor gross findings were evident in rats (mild haemorrhage of gastric mucosa at 600 mg/kg/day for 4 weeks; approximately 6 times the clinical AUC). In dogs, effects on the gastrointestinal mucosa were more overt with at doses. There was evidence of erosion in the stomach and duodenum, as well as tarry faeces and melena, seen in a 4 week study at up to 400 mg/kg/day (in excess of the approximately 100 times the clinical AUC at 200 mg/kg/day). In rabbit embryofetal development studies, multifocal red spots and ulceration of the stomach were noted in dams that received ≥ 400 mg/kg/day during the period of organogenesis (>1000 times the daily clinical dose based on body surface area (BSA) comparison) in the preliminary study and ≥ 60 mg/kg/day in the main study (> 2.9 times the clinical AUC). In general these observations were apparent at high doses of silodosin, which attained exposures several multiples in excess of those expected under clinical

[4] Nash DT (1990). Alpha-adrenergic blockers: Mechanism of action, blood pressure control and effects on lipoprotein metabolism. Clin. Cardiol., 13, 764-772

conditions. There were no signals of irritant effects on the gastrointestinal tract noted in the PI or the RMP, thus adverse findings in animal studies are likely to reflect dose-dependent toxicities unlikely to be encountered at clinical dose levels. However, it is also noted that ulcerogenic properties of prazosin and tamsulosin have been previously documented in animal studies; thus, it is also likely that these effects have a class-related basis.

Reproductive system

Treatment-related changes were noted in reproductive tissues of both male and female animals. In male animals, these changes consisted of focal atrophy and degeneration of the seminiferous tubules. In the mouse carcinogenicity study, there were occasional incidences of benign testicular tumours (interstitial cell adenoma and gonadostromal tumour at ≥ 60 mg/kg/day), interstitial fibrosis, lymphoid infiltration and distension of the prostate coagulating gland and seminal vesicles at ≥ 20 mg/kg/day. Necropsy examinations in a rat fertility study found evidence of testicular and epididymal atrophy, as well as degeneration of seminiferous tubules and focal sloughing of spermatids at doses ≥ 200 mg/kg/day. This corresponded to significant reductions in sperm viability and fertility at the highest tested dose (600 mg/kg/kg).

Effects on fertility were more moderate in a repeated study using lower doses (≤ 20 mg/kg/day; 75–80% fertility index). Delayed maturation of the prostate and testes and absence of germinal cells in testes and epididymides were reported in dogs given ≥ 50 mg/kg/day for 13 weeks. α1-antagonists such as prazosin, terazosin and tamsulosin are known to affect male reproductive function and effects of silodosin are therefore consistent with those of other α1 antagonists.

Restoration of male reproductive function was demonstrated in a GLP rat fertility study, where it was found that, following a 2 week recovery period, impairments to fertility at 20 mg/kg/day (1.8-times the clinical AUC) were comparable to untreated control group. However, this study did not report on any abnormal histology findings in reproductive tissue and thus it remains unknown whether aberrant histology findings (testicular atrophy, degeneration of epididymides and seminiferous tubules) seen at higher doses in other studies would also be reversible upon withdrawal of silodosin. Overall, effects on the male reproductive system are considered to be mediated by the pharmacological actions of silodosin.

In females, silodosin affected oestrus cycling and induced atrophy of the uterus, hypertrophy of vaginal mucosal epithelial cell and hyperplasia of mammary glands. In the reproductive toxicity studies the prolongation or disappearance of oestrus cycles at silodosin doses ≥ 60 mg/kg/day affected fertility (discussed further in the reproductive toxicity section). Histological changes to the uterus and vagina were likely caused by increased prolactin release, as were the effects on mammary glands that in mice caused mammary tumours. This was confirmed in mechanistic studies that showed dose-dependent increases in prolactin levels following either single or repeat silodosin dosing in female rats. These females also exhibited prolonged oestrus cycling and elevated progesterone levels at the highest tested dose (150 mg/kg, PO). In males the effect on prolactin release was more evident with single than with repeated dosing of silodosin.

Similar observations were reported with tamsulosin where mammary gland tumours were attributed to elevated prolactin levels that resulted from an anti-dopaminergic effect by tamsulosin on D2 receptors. In the current submission, in vitro receptor screen studies identified only a very weak affinity by silodosin for D2 receptors (although modest affinity was noted with KMD-3293: Ki 6.5 μM). Nevertheless, rodents are known to be sensitive to agents interfering with the pituitary: hypothalamic axis via an anti-dopaminergic action, and the resultant treatment associated sequelae (disturbances to oestrus cycling, increased vaginal mucification, uterine atrophy, mammary gland hyperplasia/neoplasia,

Leydig cell hyperplasia/neoplasia in males).[5] It is not clear if these observations have any clinical relevance. According to the approved US PI for silodosin, elevated prolactin levels were not seen in clinical trials; thus, silodosin is not likely to cause disturbances to prolactin secretion and increase the risk of pathologies associated with hyperprolactinaemia.

Clinical signs

The clinical effect profile of silodosin was consistent across the tested species and was typical of nonclinical observations with other α1 adrenoceptor inhibitors (tamsulosin, prazosin, terazosin, alfuzosin) currently registered in Australia. Clinical signs included ptosis, increased lacrimation and salivation, reddened ears and eyes due to increased peripheral vasodilatation and visibility of the nictitating membrane in dogs. These effects were noted almost immediately after dosing and often decreased in frequency over time with repeated dosing. However, at higher doses the severity of these toxicities was greater and included decreased locomotor activity, shallow breathing, unsteady gait and tremors. Overall, these clinical signs are α1 adrenoceptor mediated class effects and under conditions of clinical use where plasma exposures are substantially lower than those achieved in toxicity studies, the onset and severity of such effects is expected to be very low.

Genotoxicity

Not all of the submitted genotoxicity studies were conducted under GLP conditions. However, the methods used to assess genotoxicity were generally appropriate and utilised study designs that were consistent with ICH guidelines on genotoxicity testing[6] (3BS6a). With regard to assay findings, silodosin tested negative for mutagenicity in a bacterial reverse mutation assay and a mammalian forward mutation test. It was also negative in (an in vivo) mouse micronucleus assay and a rat liver DNA repair assay. Exposures attained in the in vivo studies were considered adequate based on mortalities or clinical signs as indications of moderate to severe toxicity. Slight increases in chromosomal aberrations in mammalian cells (under in vitro conditions, in the presence of metabolic activation) were associated with increases in cytotoxicity and limited solubility. Overall, on a weight of evidence basis, silodosin is not considered to be genotoxic. Genotoxicity assessments (bacterial reverse mutation and chromosomal aberration assays) on the unique human metabolite, KMD-3213G (glucuronidated silodosin) were also negative.

Carcinogenicity

The sponsor submitted two life-time carcinogenicity studies in rodents. Silodosin was administered through the diet and both males and females were used in the studies. A number of feasibility studies were presented that confirmed that the test article was adequately palatable to rodents. Design aspects of the studies were generally consistent with ICH and EU guidance for carcinogenicity studies, although historical data were not appended to studies even where reference to historical data ranges was made. Dose selection was based on preliminary toxicity studies that sought to determine a maximum tolerated dose for the tested species. In mice, a 200 mg/kg/day (subsequently reduced to 100 mg/kg/day in Week 27) dose was selected as the high dose for the main study based on lower body weight gains (≥ 30% lower than control groups) seen at doses > 200 mg/kg/day. In rats reduced body weight gain in males given with 500 mg/kg/day was the basis for selecting 150 mg/kg/day as the high dose for males and 250 mg/kg/day for females in the main carcinogenicity study. In both species mortality/survival rates were not significantly affected by silodosin treatment relative to untreated control groups. Also

[5]Hargreaves & Harleman (2011). J. Appl. Toxicol., 31, 599-607.
[6]Rules Governing Medicinal Products in the European Union - EudraLex - Medicinal products for human use, 1998 Edition: Volume 3B - Safety and the Environment - 3BS6A. Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.

negative overall findings in the genotoxicity tests allude to non-genotoxic aetiology for the neoplastic findings.

In mice, silodosin treatment was associated with significantly higher incidences of mammary gland (adenocarcinoma and adenoacanthoma) and pituitary gland (adenoma and pars distalis carcinoma) tumours in females and benign testicular tumours in males (Leydig cell adenoma, gonadostromal tumour). Mammary tumours were also associated with other non-neoplastic proliferative changes such as lobular hyperplasia, squamous metaplasia and acinar dilatation that was strongly associated with silodosin treatment.

There were also corresponding non-neoplastic cellular changes in the pituitary (increased hypertrophy, diffuse and focal hyperplasia in pars distalis pituitary). Tumours were seen at doses ≥ 150 mg/kg/day in females (≥ 41 times the clinical AUC at the MHRD), while in males benign testicular tumours were seen at doses ≥ 60 mg/kg/day (≥ 5 times the clinical AUC at the MHRD). As elaborated earlier, the mammary gland (and pituitary gland) tumours are almost certainly due to pharmacologically mediated hyperprolactinaemia, also seen in other α1 adrenergic receptor antagonists exerting anti-dopaminergic activity against D2 receptors that modulate prolactin release. Overexpression of prolactin within mammary epithelial cells has been shown to induce mammary gland proliferation and neoplasias in transgenic mice.[7]

Drug-induced hyperprolactinaemia may increase hyperplasias/neoplasias in mammary glands but also alter gonadotropin release and induce the development of neoplasms in pituitary glands and other reproductive tissue(for example, Leydig cells).[8] In contrast to humans, prolactin has luteotrophic effects in rodents and can affect fertility and also exhibits synergism with progesterone and oestrogen with respect to mammary tumour formation.[8] Evidence linking hyperprolactinaemia to breast cancer development in humans is limited although there is some renewed evidence to suggest that local production of prolactin by mammary cells may have a role; however more research is needed to define this association.

Based on text used in the approved US label for silodosin (Rapaflo), it is recommended that the sponsor includes a statement in the 'Carcinogenicity' section that states elevations to prolactin levels were not seen in clinical trials with silodosin.

In rats, silodosin caused a treatment-dependent increase in thyroid tumour development (follicular cell adenoma and carcinoma) that was more prevalent in males than females. Associated findings included significant increases in thyroid (and parathyroid) weights and follicular cell hypertrophy. These findings were apparent at doses ≥ 50 mg/kg/day for males (5.1 times the clinical AUC at the MRHD) and 250 mg/kg/day in females (21 times the clinical AUC at the MRHD). Aside from lower body weight gain at high doses and increased liver weights, there were no other significant findings associated with silodosin treatment.

Two mechanistic studies were conducted to identify the mechanism behind the thyroid effects in rats. In the first study, male rats were exposed to silodosin (150 and 300 mg/kg/day) for 4 weeks wherein the treatment-related increase in liver weights was associated with elevations in microsomal protein content compared to control, specifically T4 glucuronosyltransferase content and activity. This in turn correlated to alterations in thyroid hormone levels, such that levels of thyroid stimulating hormone (TSH) were decreased while T4 levels were slightly but significantly increased in the 300 mg/kg dose group. In the second study the effects of silodosin on liver and thyroid weights and histology were similar to those of the known liver inducer phenobarbital. Measurement of thyroid hormones indicated slight increases in TSH levels and significant decreases in T4

[7]Rose-Hellekant et al., (2003). Oncogene, 22, 4664-4674.
[8]Wu & Farrelly (2006). Am. J. Therap., 13, 141-144

levels, which resolved following the recovery period. Most of the findings resolved following a 4 week recovery period, although the incidence and severity of follicular cell hypertrophy was still higher in the treated groups compared to controls. As the silodosin-induced changes paralleled those of phenobarbital it is highly probable the same mechanism is responsible for the thyroid changes and indeed thyroid tumours induced by silodosin. Thyroid tumours accompanied by hepatocellular hypertrophy are commonly seen in rodents exposed to drugs that interfere with thyroid hormone clearance and are not considered relevant to humans as rodents are more sensitive to changes in thyroid hormone clearance than humans.

Reproductive toxicity

Reproductive toxicity was evaluated in fertility, embryofetal development and pre-/postnatal development studies in rats and in embryofetal development in rabbits. Animals received daily oral doses of silodosin of up to 1000 mg/kg/day in rats and up to 600 mg/kg/day in rabbits. The study designs were generally acceptable, using accepted dosing regimens appropriate for the selected test species. However, a number of studies were not GLP compliant. Preliminary dose-range finding studies were performed to determine an appropriate dose range for the main reproductive toxicity study. Toxicokinetic parameters for the reproductive toxicity studies were only determined in the main embryofetal development study in rabbits. As well, the potential placental and milk transfer of silodosin was not assessed. Relative exposures are summarised in Table 3.

Relative exposure

Table 3: Relative exposure in reproductive toxicity studies

Species	Study	Dose mg/kg/day	AUC0–t h ng.h/mL	Exposure ratio#
Rat (SD)	Fertility [10026^]	20	701/532^	1.8/1.3
		60	2568/1858^	6.5/4.7
		200	11151/4106^	28/10
		600	24241/7519^	61/19
	Embryofetal development [10026^]	20	532	1.3
Rabbit (NZW)	Embryofetal development [10116*]	20	209*	0.53
		60	1131*	2.9
		200	9056*	22.8
Human (healthy male subjects)	Steady state	8 mg/day for 7 days	396	–

= animal AUC_{0-th}: human plasma AUC_{0-24h}; ^AUC values were calculated as AUC_{0-4h}; *AUC values were calculated as $AUC_{0\,6h}$;

The sponsor did not conduct extensive toxicokinetic assessments for the reproductive toxicity studies, relying largely on existing data from other toxicity studies where appropriate. There were also no investigations conducted to establish whether silodosin passed through the placenta or into milk. The sponsor did not offer a justification but presumably this was because silodosin is not intended to be used in female patients and therefore use during pregnancy is not anticipated.

Fertility effects were assessed in rat studies where treated males and females were paired with untreated animals. Except for a low dose male-only fertility study, all studies were non-GLP. In the preliminary studies higher dosing was utilised (20, 60, 200 and 600 mg/kg/day; 1.8 to 61 times the clinical AUC at the MRHD). There were no treatment-related mortalities in these studies and clinical signs were consistent with those seen in other studies (increased lacrimation and salivation, ptosis), along with decreases in weight gain seen in at the highest tested dose (600 mg/kg/day or 61 and 19 times the clinical AUC for males and females, respectively).

Fertility was compromised at all doses and in both males and females. Disturbances to male sexual function by α1 adrenoceptors are well known and are due to an inhibitory action on vas deferens contractility which reduces sperm content in ejaculate[9] and subsequent infertility. It is not entirely clear whether inhibition of ejaculatory function alone was responsible for the effects on fertility in these studies as histopathology examinations also showed testicular atrophy at 600 mg/kg (that is, at 61 times the clinical AUC) and dose dependent sloughing of spermatids. In the main GLP study where lower silodosin doses were used (≤ 20 mg/kg/day), there were no abnormal necropsy findings and impairments to fertility at 6 and 20 mg/kg/day were reversible, as indicated by a restoration of the fertility index to vehicle control levels following a 2 week recovery period. In females, impairments to fertility were associated with disturbances to oestrus cycling. As discussed above these disturbances were likely secondary to alterations to prolactin secretion which in turn affected gonadotropin levels that govern oestrus cycles. The No observable adverse effect level (NOAEL) for male fertility was determined to be at 2 mg/kg/day, which resulted in dose exposures that were 2.3 times the human dose based on body surface area comparisons (since plasma measurements were not available for doses < 20 mg/kg). The NOAEL for female fertility was 20 mg/kg/day, which resulted in exposures that were 1.3 times the clinical AUC. Overall, silodosin is predicted to affect fertility in males and females through a pharmacologically mediated mechanism. Effects on male fertility are likely to be reversible at clinical exposures. Effects on female fertility are unknown; however, silodosin is not proposed for use in women.

Embryofetal development studies were conducted in rats and rabbits where silodosin was administered to pregnant animals during the period of organogenesis. In rats, doses of silodosin of up to 1000 mg/kg had no effect on litter parameters or on fetal development. Toxicokinetic measurements were not carried out; however, maternal clinical signs were consistent with those of other toxicity studies (that is, ptosis, increased lacrimation and salivation) and gave some assurance on the adequacy of exposure. On the other hand, the adequacy of fetal exposures to silodosin is unknown as there were no data available on placental or milk transfer of silodosin. In rabbits, silodosin was maternotoxic at doses ≥ 200 mg/kg, causing decreases in body weight gain and food consumption, as well as signs of gastric irritation and increased incidences of abortions. Examination of fetuses did not reveal any significant evidence of fetal malformations. There was one fetus from a 200 mg/kg dosed dam with developmental abnormalities (gastroschisis, anury, anal atresia and club foot) but this was considered an isolated incident since no other litter mates or other pups at this dose of silodosin and higher exhibited signs of abnormal development.

Litter parameter assessments however revealed a treatment-dependent decrease in fetal viability at 200 mg/kg/day (23 times the clinical AUC at the MRHD) with higher fetal losses through either abortions or fetuses found dead at term. Overall, in rats the NOAEL for embryofetal development was 1000 mg/kg/day (> 1000 times clinical exposures at the MRHD based on body surface area comparisons), while in rabbits the NOAEL was 60 mg/kg/day (2.9 times the clinical AUC), bearing in mind that these effects were secondary to maternotoxicity.

[9] Ratnasooriya & Wadsworth (1994). Andrologia, 26, 107-110

In the rat pre/postnatal development study doses of up to 600 mg/kg/day were used. Maternal mortalities were evident at doses ≥ 100 mg/kg/day and were likely treatment-related as necropsy assessments indicated multifocal haemorrhaging in the liver and stomach. Litter parameters in the preliminary study showed significantly higher incidences of stillborn pups in the 30 and 100 mg/kg/day dose groups but in the absence of a dose dependent relationship it is uncertain whether these observations are treatment-related.

In the main study there were no statistically significant differences in litter parameters between controls and treatment groups. However there were findings that suggested treatment related effects on development: in the preliminary study impairments to suckling ability were reported in pups from the 300 and 600 mg/kg/day dose groups, while in the main study impaired ambulation was noted in F1[10] males from the 300 mg/kg/day dose group. There were no other developmental effects with growth milestones and reproductive performance being comparable between F1 generation offspring from treated and untreated control groups. For both studies the NOAEL for pup development was determined to be 100 mg/kg/day (approximately 14 times the clinical AUC at the MRHD; based on rat AUC value for 125 mg/kg/day).

Pregnancy classification

The sponsor nominated Pregnancy Category B3[11] in the proposed PI but prefaced this by stating that silodosin is intended for male patient use only. Although there was no evidence of treatment-associated teratogenicity in either rats or rabbits, there were fetal losses (albeit, at maternotoxic doses) and evidence of impairments to neonatal development which would be considered to be evidence of fetal/neonatal harm. For this reason the proposed category is considered acceptable. Text accompanying the 'Use in Pregnancy' section of the PI however should be amended.

Local tolerance

The local effects of silodosin administered by the intramuscular route were examined in male rabbits. Silodosin caused mild reactions characterised by slight local haemorrhaging, mild oedema and necrosis of muscle fibres in the surrounding areas of administration. Administration sites exhibited relatively quick recoveries compared to positive control article, with the only notable changes being mild signs of muscle regeneration. With regard to the clinical (oral) route, in some studies there was occasional evidence of irritation to the gastrointestinal mucosa (erosion, ulceration and haemorrhage of gastric mucosa, haemorrhagic area in caecum and duodenum, and bloody stools) that tended to be seen in preliminary studies where higher dosing was used. The utility of the tolerance studies using a parenteral route are uncertain given the fact that the clinical product is administered orally. Nevertheless, findings from both the tolerance study and toxicity studies suggest that silodosin may be a mild irritant depending on dose. Silodosin did not exhibit antigenic or haemolytic properties.

Phototoxicity

Distribution studies in rats (albeit, albino Sprague-Dawley (SD) rats) did not identify affinity of silodosin for pigmented tissues (skin or uveal tract). Nevertheless, based on its spectral attributes (peak absorbance at 269 nm and 332 nm with molar absorption coefficients of 9343 and 3284 mol-1cm-1, respectively), phototoxicity studies were

[10] The F1 generation is the generation resulting immediately from a cross of the first set of parents (parental generation).
[11] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

conducted under in vitro and in vivo conditions. Using a Neutral Red uptake (cell viability) assay, silodosin treated cells that were exposed to ultraviolet (UV) irradiation exhibited impaired uptake of the marker, signifying cell damage. However, the extent of cell damage was not as great as reference control substance CPZ (as reflected by Photo Irritation Factor (PIF) values > 10 for CPZ compared to < 5 for silodosin). The ICH guideline on phototoxicity[12] considers a PIF value ranging between 2 and 5 to be of questionable toxicological relevance for systemic drugs and generally advises against further photo safety evaluations. Nevertheless, the sponsor conducted a follow-up in vivo investigation in mice that were dosed with silodosin and exposed to UV irradiation. These studies showed that silodosin caused mild skin reactions (minimal grade erythema) that generally resolved by the next day following treatment. The mild reaction suggests that silodosin is photoreactive but unlikely to evoke a significant and clinically relevant reaction.

Metabolites

Toxicological qualification of the unique human metabolite KMD-3213G (glucuronidated silodosin) was provided in a series of toxicity studies. KMD-3213G tested negative for mutagenicity and clastogenicity in in vitro genotoxicity studies (reverse bacterial mutation assay, chromosomal aberration test in Chinese hamster lung cells). Acute and chronic toxicities of KMD-3213G were assessed in a series of studies where MD127K and/or its vehicle (0.5 M citric acid buffer) were administered intravenously, either as a single dose or daily for a two week period. Although silodosin is proposed for oral administration, the intravenous route was likely used for these studies to ensure that maximal systemic exposure was attained without interference by intestinal biotransformation (that is, deconjugation). The adequacy of using a 2 week dosing period is uncertain in view of the likely intermittent/chronic use profile.

Aside from clinical signs that were consistent with those seen with silodosin (such as ptosis, increased lacrimation and deep respiration), there were no other toxicity findings directly related to KMD-3213G treatment. Mortalities were high in the acute toxicity study with either KMD-3213G or vehicle and likely reflected the dose volume limiting toxicity of 0.5 M citric acid buffer. Findings from the two week toxicity study in which the toxicity profiles of silodosin and KMD-3213G were compared indicated mostly incidental changes that could not be immediately distinguished as treatment-related. There were no treatment-related mortalities or changes to body weight and only minor incidental findings were noted in necropsy assessments on the two treated groups. Exposures attained relative to levels of KMD-3213G and silodosin expected under clinical conditions were sufficiently high in view of the lack of notable findings (≥ 12 times and ≥ 30 times the human AUC values for KMD-3213G and silodosin, respectively; based on clinical values from Study No. IT-PK-0241 in non-elderly patients). Overall, the unique human metabolite KMD-3213G is considered toxicologically qualified.

Impurities

The proposed limits for the identified metabolites KMD-3241 and KMD-3289 in silodosin drug product were ≤ 1.0% and ≤ 0.3%, respectively. The limit for KMD-3289 is below the ICH qualification threshold and does not require further toxicological qualification while the limit for KMD-3241 is above the qualification threshold (80 µg/day at ≤ 1.0% compared to ≤ 50 µg total daily intake). However, as both entities are human metabolites and have been detected in rats under in vivo conditions, both impurities are considered qualified.

Paediatric use

Silodosin is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

[12] ICH S10Guidance on photosafety evaluation of pharmaceuticals.

Nonclinical summary and conclusions

- The submitted nonclinical dossier was in general accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals.[2] All the pivotal safety and toxicity studies were conducted according to GLP. The overall quality of the dossier was acceptable in view of the design and scope of the submitted studies.
- Silodosin binds to the α1A AR subtype with nanomolar affinity (pKi 10.4 recombinant human), but has lower affinity for α1B and α1D subtypes than reference α1 antagonists, prazosin and tamsulosin. Under in vitro conditions silodosin inhibited noradrenaline-mediated prostatic smooth muscle contractions to a similar extent as tamsulosin. In a rat model of BPH silodosin attenuated phenylephrine-induced increases in intraurethral pressure to a similar extent as tamsulosin. The potency of silodosin against α1 AR- contractions in aorta and spleen was lower than tamsulosin and prazosin. The major human metabolite KMD-3213G (glucuronidated silodosin) exhibited similar pharmacological activity to the parent drug.
- Off-target effects of silodosin included significant binding to 5-HT1A receptors (Ki 0.31 nM), moderate binding to 5-HT subtypes 1B, 1D and 7, and to β2 receptors (Ki 5.7 nM), and weak binding to dopaminergic D3 receptors (Ki 350 nM). As a chiral substance, pharmacological characterisation studies on the S-enantiomer of silodosin were not conducted. In vivo studies found no evidence of enantiomer interconversion in rats or dogs.
- Specialised safety pharmacology studies showed minimal changes to CNS and respiratory parameters and no treatment related effects on ECG parameters in conscious dogs. In vitro studies (inhibition of hERG tail currents, increased action potential duration) and a dog toxicity study (prolonged QT intervals) only showed adverse effects on the cardiovascular system at relative exposures much higher than those expected under clinical conditions. The major human metabolite, KMD-3213G, had no effect on CNS, cardiovascular or respiratory parameters.
- Silodosin is rapidly absorbed in rats and dogs, while in humans absorption is slower (T_{max} approximately 0.1-1.7 h compared to 1.5-3.0 h, respectively). Protein binding is higher in human plasma than rat or dog plasma (95% as compared to approximately 80% and 82% in rat and dog plasma, respectively). Silodosin was extensively distributed in rat tissues except for the CNS. CYP 3A4 mediated oxidation of silodosin generates metabolites KMD-3241, KMD-3289 and KMD-3310, while alcohol and aldehyde dehydrogenases generate KMD-3293 and KMD-3295. These metabolites are common to rats, dogs and humans, with KMD-3293 identified as a major metabolite in humans. Glucuronidation by UGT 2B7 generates the human metabolites KMD-3213G and KMD-3241G. The primary excretion route was faecal in all species and likely involved biliary excretion. Overall, qualitative differences between the pharmacokinetic profiles of humans and test species are not considered significant enough to limit the utility of silodosin toxicity assessments in test species.
- Silodosin and major human metabolites KMD-3213G and KMD-3293 did not show clinically significant inhibitory activity against CYP isozymes or evidence of enzyme induction. Elevated microsomal protein content observed in toxicity studies was a rodent-specific response. Silodosin is a substrate of P-glycoprotein (P-gp) but potential P-gp inhibitory activity was not assessed. No specific interaction potential was identified but in view of the role of CYP3A4 in hepatic clearance of silodosin, caution is advised when co-administered with strong CYP3A4 inhibitors.
- Silodosin exhibited a moderate order of acute toxicity in rats and dogs.
- Repeat dose oral toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 52 weeks in dogs were conducted. Plasma exposures were moderate in rats and high in

dogs. Target organs for toxicity included the liver (increased organ weights, swelling, yellow-brown pigment deposits, fatty-associated degeneration of hepatocytes, elevated AST and ALT) and the gastrointestinal tract (mild to moderate erosion, ulceration and haemorrhagic foci of gastric, duodenal and jejunal mucosa and petechiae in stomach). Treatment related changes were also noted in male and female reproductive tissue (focal atrophy of seminiferous tubules, interstitial cell fibrosis, testicular and epididymal atrophy; disrupted oestrus cycling, uterine atrophy, increased vaginal mucification and mammary gland hyperplasia) that were likely secondary to hyperprolactinaemia caused by the anti-dopaminergic actions of silodosin.

- On a weight of evidence basis, silodosin was not considered to be genotoxic. It was negative in a bacterial reverse mutation assay, a mammalian forward mutation test, an in vivo mouse micronucleus test and in a rat liver DNA repair assay. Slight increases in chromosomal aberrations in the in vitro clastogenicity assay coincided with increases in cytotoxicity and limits to solubility. The unique human metabolite KMD-3213G also tested negative for genotoxicity.
- Higher incidences of mammary gland tumours (adenocarcinoma, adenoacanthoma) were seen in mice and were secondary to drug-induced hyperprolactinaemia. Exposures at the NOEL were 0.8 and 6.4 times the clinical AUC for male and female mice, respectively. In rats silodosin induced thyroid tumour development (follicular cell adenoma and carcinoma) was observed at exposures that were 5 and 21 times the clinical AUC at the MRHD in males and females, respectively. These tumours corresponded to increased T4 glucuronosyltransferase levels in liver and are known to be a rodent specific pattern of tumour development not relevant to humans.
- Silodosin adversely affected both male and female fertility at doses ≥ 6 mg/kg/day in males and >20 mg/kg/day in females. In both cases the effects were pharmacologically mediated and in males, fertility was restored once silodosin treatment was withdrawn. Silodosin was not teratogenic in rats or rabbits but there was evidence of overt increased fetal losses and impairments to neonatal development. Fetal losses were secondary to signs of maternotoxicity.
- The proposed limits for two specified impurities in the silodosin drug product are considered adequately qualified.

Nonclinical conclusions and recommendation

- Primary pharmacology studies adequately support the proposed use of silodosin for the treatment of BPH.
- Silodosin displayed moderate off-target affinity for 5-HT1A, 1B, 1D and 7, β2 and dopaminergic D3 receptors. Specialised safety pharmacology studies did not identify any clinically significant hazards.
- Silodosin metabolism is dependent on CYP 3A4, alcohol and aldehyde dehydrogenase and UGT 2B7. Silodosin is also a substrate of P-gp. Drugs that affect P-gp and these enzymes may affect the clearance of silodosin.
- The key target organs for toxicities were the liver, the gastrointestinal tract and the reproductive organs. Effects on the liver and reproductive organs are likely rodent-specific response to the pharmacological actions of silodosin; although, postmarketing data have identified incidences of hepatobiliary disorders. Irritation in the gastrointestinal tract occurred at higher doses than those expected with clinical use.

- Silodosin was not genotoxic. Carcinogenicity studies indicated that tumour development (mammary tumours in mice, thyroid tumours in rats) was secondary to rodent-specific hormonal disturbances induced by silodosin.
- The proposed Pregnancy category of B3 is considered appropriate for silodosin.
- There are no nonclinical objections to registration of silodosin.
- The nonclinical sections in the draft PI require amendments.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

α -blockers were developed for the treatment of hypertension, but their use for BPH is limited by orthostatic hypotension. α1b-receptors are located mainly in the cardiovascular system, while α1a-receptors are located mainly in the lower urinary tract. Silodosin is a α1a-blocker which acts on the smooth muscle of the prostate, urethra and trigone of the urinary bladder. It has high selectivity with a α1a:α1b binding ratio of 162:1, with the potential to have fewer effects on systemic blood pressure than non-selective α-blockers. It is marketed in many jurisdictions for the treatment of irritative and obstructive symptoms associated with BPH.

Contents of the clinical dossier

Scope of the clinical dossier

The present submission comprises 31 clinical pharmacology studies of which 24 contain pharmacokinetic (PK) data and a further 10 contained PD data. In addition, a single population PK (PopPK) analysis was included as part of the evaluation materials.

There were nine clinical studies consisting of three pivotal Phase III efficacy studies; a single Phase II efficacy study; three open-label, long-term extension studies (EU and US); and two efficacy and safety studies in Japanese patients.

Pivotal efficacy studies submitted:

- SI04009: a double-blind, randomised, Phase III comparison of silodosin 8 mg and placebo given for 12 weeks (US)
- SI04010: an identical, double-blind, randomised, Phase III comparison of silodosin 8 mg and placebo given for 12 weeks (US)
- KMD3213-IT-CL-0215 (IT-CL-0215): a double-blind, randomised, Phase III, non-inferiority comparison of silodosin 8 mg, tamsulosin 0.4 mg and placebo given for 12 weeks (EU)

Other studies submitted:

- KMD3213-US021-99-99 (US021-99): a double-blind, randomised, Phase II comparison of silodosin 4 mg, silodosin 8 mg and placebo given for 8 weeks (US)
- An Integrated Summary of Efficacy (US patients)

- SI04011: an open-label, long-term efficacy and safety study of silodosin 8 mg given for 40 weeks (US)
- KMD3213-IT-CL-0215 (OLE): an open-label extension study of silodosin 8 mg given for 40 weeks (EU)
- KMD-203: a long-term, safety and efficacy study of silodosin 4 mg/day (2mg bid) and silodosin 8 mg/day (4mg bid) given from 28 to up to 52 weeks (Japan)
- KMD-303: a Phase III, double-blind, parallel group, active and placebo controlled study of silodosin 8 mg/day (4mg bid), tamsulosin 0.2 mg/day (0.2 mg qd) and placebo given for 12 weeks (Japan)
- KMD-305: a Phase III, open-label, study of silodosin 4 mg/day (2 mg bid) and 8 mg/day (4 mg bid) (or silodosin 2 mg/day if not tolerated) given for 52 weeks (Japan)
- IT-CL-IT-CL-0376: an open-label Phase 4 study of silodosin 8 mg given for 24 weeks (EU)

Paediatric data

No clinical studies have been performed in children.

Good clinical practice

The US and Europe studies were conducted according to the principles of ICH Good Clinical Practice (GCP). Studies performed in Japan were performed according to local regulations.

Pharmacokinetics

Studies providing PK data are listed below.

Table 4: Studies providing PK data

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	SI07004	Dose-proportionality of silodosin and silodosin-G and KMD-3293 after one and seven daily doses of 4 and 8 mg
	Food and bioavailability	KMD-308	Effect of food on the PKs of a single, 4mg oral dose of silodosin and bioavailability compared with a 2 mg, IV dose
	Single dose PKs	95283	PKs of a single administration of 0.5 to 2.5 mg silodosin in Japanese males
		98363	PKs of silodosin and metabolites in Japanese males
		UK01-97	Plasma and urine PKs of single oral doses of silodosin

PK topic	Subtopic	Study ID	*
	Multi-dose PKs	UK02-97	Plasma and urine PKs of multiple oral doses of silodosin
		98364	PK and safety following repeat doses in Japanese males
		SI06004	PKs of silodosin and four metabolites following administration of silodosin 8 mg once daily for 7 days.
	Therapeutic and supra-therapeutic doses	SI05014	Effect of 8 mg or 24 mg on the time-matched changes from baseline in the corrected QT interval
		SI05008	Determine the maximum tolerated dose of silodosin
	Time of dosing	95284	PKs following administration of 1.5 mg for three times a day
	Mass balance	US012-99	Define plasma and whole blood concentration versus time curves for total radioactivity and mass balance following oral administration of [^{14}C]-silodosin
PKs in Special Populations	Renal impairment	KMD-309	PKs of a single oral dose in subjects with impaired renal function
		IT-PK 0234	PKs of silodosin in subjects with different degrees of renal impairment and in healthy subjects
	Hepatic impairment	SI05010	PKs of silodosin and major metabolites in subjects with moderate liver dysfunction
	Elderly	KMD-105	PKs of silodosin following a single oral administration in elderly male and non-elderly male
		IT-PK 0241	Assess exposure at steady-state of silodosin in 2 groups of elderly subjects, 65-75 and >75 years of age respectively, in

PK topic	Subtopic	Study ID	*
			comparison with that of younger subjects
		KMD-207	Assess repeat dosing of 12 mg/day (6 mg/dosing, twice daily) in males from the age group of patients with BPH
		US011-98	Assess multiple oral doses healthy males of the target age (between 50 and 70)
PK interactions	Diltiazem	IT-PK 0242	Assess the effects of diltiazem on the silodosin PKs in healthy male
	Digoxin	IT-PK 0263	Effect of silodosin at steady-state on the steady-state PKs of digoxin
		KMD-307-UK	Effect of steady-state silodosin on the steady-state PKs of digoxin
	Ketoconazole	KMD-306-UK	Effect of multiple oral doses of a ketoconazole on the PKs of single oral doses of silodosin
		SI06008	Effect of multiple oral doses of 400 mg ketoconazole on the PKs of a single 8 mg oral dose of silodosin

* Indicates the primary PK aim of the study.

Evaluator's conclusions on pharmacokinetics

Limitations of the PK studies

- No dedicated PK studies examined the bioequivalence between batches of silodosin manufactured using the different formulation methods used in the clinical studies. In addition, no studies examined the bioequivalence between batches of silodosin formulated according to Method C from the different companies.
- No dedicated clinical studies examined the bioequivalence between the 4 mg and 8 mg dose strength capsules proposed for marketing.
- Neither bd nor td dosing has been examined using the proposed formulation for marketing (formulation C).
- Although some limited analysis examining drug accumulation was undertaken as part of the Phase III Study KMD-305, no dedicated PK studies examined silodosin PKs in the target population (males with BPH).

Questions regarding the PK studies

- Can the sponsor please indicate where the proposed product for marketing will be manufactured and by whom?
- The PK/PD evaluator has been unable to find any discussion of the type of meal given to the subjects in the KMD-308 Study Report when they were administered silodosin under non-fasting conditions. Can the sponsor please confirm whether the meal could be considered a low- low calorie, moderate fat- moderate calorie or a high fat, high calorie meal?

For further details on the evaluator's conclusions on PK see Attachment 2.

Pharmacodynamics

The following table provides a list of studies that provided pharmacodynamic (PD) data.

Table 5: Studies providing pharmacodynamic data

PD Topic	Subtopic	Study ID	*
Primary Pharmacology §	Effect on subjective symptoms, objective finding, QOL and IPSS	KMD-201	Correlation of dose and efficacy patients with dysuria associated with BPH
		KMD-202	Efficacy following administration as two divided doses of 4 mg/day or 8 mg/day in patients with micturition disorder associated with BPH
		KMD-206	Effect of two-divided doses of 8 mg/day on voiding function in patients with micturition disorder associated with BPH
PD Interactions	Sildenafil or tadalafil	SI06002	Orthostatic effects following co-administration of a single dose of 100 mg sildenafil, 20 mg tadalafil or placebo, after multiple dose doses of 8 mg silodosin in healthy target-aged males
	Metoprolol	SIL0901	Orthostatic effects following co-administration of 8 mg silodosin and 50 mg metoprolol
	Amlodipine	SIL0902	Orthostatic effects following co-administration of 8 mg silodosin and 10 mg amlodipine.
	Lisinopril	SIL0903	Orthostatic effects following co-administration of 8 mg silodosin and 20 mg lisinopril

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacodynamics

Mechanism of action

- Silodosin is a highly selective α1A-adrenoceptor antagonist. In the urogenital system α1A-blockade results in decreased bladder outlet resistance without affecting detrusor smooth muscle contractility.

Primary pharmacodynamic effects

- All of the primary PD studies only examined cohorts of Japanese patients and none of the studies used the proposed dosing regimen.
- In patients with BPH, silodosin (form A) at doses of 0.1 mg, 1 mg or 2 mg twice a day induced a non-clinically significant, dose-dependent improvement in subjective symptoms and quality of life (QoL) due to urinary symptoms.
- Compared to placebo, administration of silodosin as two divided doses of either 2 mg/day (for a total of 4 mg/day) or 4 mg/day (for a total of 8 mg/day) induced an improvement in subjective symptoms, which was high in the 4 mg/day group and even higher in the 8 mg/day group; however, the differences observed were not statistically significant.
- In patients with micturition disorder associated with BPH, administration of silodosin in two divided doses of 8 mg/day, 50% of treated subjects reported an effective rate of improvement in subjective symptoms and QoL, whereas, only 10% had an effective rate of improvement in peak urine flow rate.

Secondary pharmacodynamic effects

- Silodosin and its two active metabolites appear to have no meaningful effect on heart rate (HR), PR and QRS interval[13] duration or on cardiac repolarisation.
- Following administration of doses of silodosin ranging from 1 mg to 16 mg, positive orthostatic tests (both Type I and II) were more prevalent in subjects administered silodosin than those given placebo.

Time course of pharmacodynamic effects

- Improvements in subjective symptoms, QoL and objective findings occurs following 2 to 4 weeks treatment with silodosin, with some evidence suggesting that the improvement during the first 2 weeks of treatment was generally larger than that experienced in the second 2 weeks.

Pharmacodynamic interactions

- Following administration of silodosin in combination with sildenafil (100 mg), tadalafil (20 mg), metoprolol (50 mg) or amlodipine (10 mg), no clinically meaningful changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were identified.
- Although there were no clinically significant changes in SBP or DBP when an 8 mg dose of silodosin was co-administered with 20 mg lisinopril, more positive orthostatic tests relating to HR were identified during the silodosin phase (62 versus 38) than in

[13] In electrocardiography, the PR interval is the period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization); it is normally between 120 and 200ms in duration. The PR interval is sometimes termed the PQ interval.

the placebo phase. Overall, 79 positive tests were observed during the silodosin/lisinopril phase (79/252; 31.3%), whereas, 40/252 positive tests were observed during the placebo/lisinopril phase (15.9%).

Dosage selection for the pivotal studies

The 8 mg dose of silodosin was based on multiple pre-clinical and clinical pharmacology studies. In the dose finding study US021-99, efficacy was marginally superior in the 8 mg group compared with 4 mg group (see Attachment 2 Section 7), while safety and tolerability were comparable for the two doses. The data support the use of the 8 mg dose, with the option to reduce the dose to 4 mg if necessary.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies:

- SI04009: a double-blind, randomised, Phase III comparison of silodosin 8 mg and placebo given for 12 weeks (US)
- SI04010: an identical, double-blind, randomised, Phase III comparison of silodosin 8 mg and placebo given for 12 weeks (US)
- KMD3213-IT-CL-0215 (IT-CL-0215): a double-blind, randomised, Phase III, non-inferiority comparison of silodosin 8 mg, tamsulosin 0.4 mg and placebo given for 12 weeks (EU)

Evaluator's conclusions on efficacy

The three pivotal silodosin efficacy studies were conducted with a conventional randomised, double-blind, placebo-controlled, parallel group design together with an active control in the EU study. The results were consistent, with decreases in International Prostate Symptom Score (IPSS) total score for the primary endpoint of -6.5 to -7.0 in the silodosin groups of the pivotal studies and -6.5 in the tamsulosin group in the EU study. Changes in the placebo groups ranged from -3.4 to -4.7 and the differences compared with the active treatment groups were each highly statistically significant (range -2.3 to -2.9, $p<0.0001$). In the EU study there was also convincing statistical evidence for non-inferiority of silodosin compared with tamsulosin.

Analyses for the secondary endpoints were consistent with those for the primary endpoint. There were modest decreases in IPSS irritative and obstructive scores and there were modest improvements in QoL in the active treatment groups compared with placebo. There were modest, statistically significant increases in maximum flow rate (Qmax) and the benefits in favour of silodosin compared with placebo were highly statistically significant. The improvement in the symptoms of BPH were rapid in onset and were sustained for at least one year, as shown in two US and EU OLE studies, in a long-term Phase III study in Japanese patients and in a Phase IV study in European patients. The outcomes were comparable across all age groups. Responder analyses (IPSS ≥ 25%, Qmax ≥ 30%) were performed only in the EU study. There were statistically significant improvements in IPSS in both active treatment groups compared with placebo. However, increases in Qmax were inconsistent and not statistically significant. The study outcomes are broadly in line with clinical trial data summarised in the Australian tamsulosin product information. Flomatra was superior to placebo given for 12 weeks in two pivotal studies. Treatment differences in IPSS total score were -1.6 (95% CI: -2.5, -0.6, p=0.0016)

in Study 617-CL-303 and -1.7 (95% CI: -2.5, -1.0, p<0.0001) in study 617-CL-307. QoL scores decreased in the first study [Odds ratio -0.4 (-0.6, -0.2) but increased in the second study [OR 1.53 (1.18, 2.0)]. The study entry criteria are not recorded.

Baseline disease characteristics (including medical histories and α blocker use at screening) are not provided in the body of the US study reports and incomplete data are provided in annex tables. These data should be provided. A significant weakness in the studies was the exclusion of placebo responders from randomisation. The sponsor was asked by the European Medicines Agency (EMA) to justify this step which enriched the study population in favour of active treatment. However, a post hoc analysis showed that this did not influence the overall conclusions of the controlled studies.

The modest treatment differences in the placebo controlled studies were highly statistically significant, but the clinical significance of the changes across studies (IPSS -2.3 to -2.9) is questionable. The sponsor proposes that the treatment benefits were clinically meaningful as a decrease in IPSS of 2 points is perceived by patients as slight improvement. In support, the sponsor cites the American Urological Association (AUA) guideline and a publication on which the guideline was based.[14] However, both citations are inaccurate. Basing their opinion on the publication, the AUA guideline states that 'a three-point improvement in the AUA-SI is considered meaningful'. The AUA guideline is supported by the outcomes of the controlled silodosin studies. In Study SI04009, patients in the silodosin group improved IPSS by -6.5 but only 33.4% of patients reported feeling 'mostly satisfied' or better. In the placebo group, the change in IPSS was -3.6 but only 23.2% of patients reported similar benefit.

The clinical relevance of the modest and inconsistent increases in Qmax is not discussed or justified by the sponsor. The sponsor should justify the relevance of the observed differences in the outcomes before the conclusions are accepted (see Clinical Questions in Attachment 2).

Safety

Studies providing safety data

There were no pivotal studies that assessed safety as the sole primary outcome.

Patient exposure

A summary of total exposure in all BPH studies is shown in Table 6. Mean exposure in the overall silodosin 8 mg Phase II-IV safety population (n=2,617) was 202.2 days. In the overall Phase II-III safety population (n=1,581), the mean exposure to silodosin was 224.0 days. In the silodosin (n=931) and placebo (n=733) arms of the controlled studies, mean exposures were 77.8 and 78.2 days, respectively. In the overall safety population, 1750 (66.87%) patients were exposed for ≥ 6 months and 393 (15.02%) patients were exposed for ≥ 1 year.

[14] Barry MJ, et al. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients? J Urol 1995; 154:1770-1774

Table 6: Summary of exposure in all clinical studies in LUTS/BPH

	Overall Silodosin Safety Population (Phase II-IV)	Overall Silodosin Safety Population (Phase II-III)	Silodosin and Placebo Safety Population (controlled clinical trials)	
	Silodosin 8 mg (N=2617)	Silodosin 8 mg (N=1581)	Silodosin 8 mg (N=931)	Placebo (N=733)
Extent of Exposure (Days)				
Mean (SD)	202.2 (106.13)	224.0 (126.12)	77.8 (20.33)	78.2 (19.61)
Median	176.0	280.0	85.0	85.0
Min, Max	1 - 471	1 - 471	1 - 107	1 - 118
N	2499	1538	927	727
Interval (Weeks)				
0 < Dur ≤ 2	57 (2.18%)	45 (2.9%)	30 (3.22%)	22 (3.00%)
2 < Dur ≤ 4	58 (2.22%)	35 (2.3%)	19 (2.04%)	14 (1.91%)
4 < Dur ≤ 12	233 (8.90%)	209 (13.6%)	274 (29.43%)	236 (32.20%)
12 < Dur ≤ 26	1028 (39.28%)	301 (19.6%)	604 (64.88%)	455 (62.07%)
26 < Dur ≤ 39	248 (9.48%)	86 (5.6%)	NA	NA
39 < Dur	875 (33.44%)	862 (56.0%)	NA	NA
Missing	118 (4.51%)	43	4 (0.43%)	6 (0.82%)
Exposure ≥ 6 months	1750 (66.87%)	961 (62.4%)	NA	NA
Exposure ≥ 1 year	393 (15.02%)	384 (24.9%)	NA	NA

Safety issues with the potential for major regulatory impact

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

ECG changes in the Phase II/III safety populations are shown in Table 7. Treatment emergent, clinically significant ECG changes were reported in 1.5% and 2.7% of the silodosin and placebo populations, respectively. No QTc safety signals were identified during a maximum tolerated dose study (SI05008), or in a Thorough QTc study (SI05014). No ECG safety signals were detected during the OLE studies.

Table 7: ECG changes in the overall silodosin and placebo safety populations

Parameter	Silodosin Overall Safety Population Silodosin 8 mg (N=1,581)	Silodosin and Placebo Safety Population	
		Silodosin 8 mg (N=931)	Placebo (N=733)
Baseline:			
Normal	826 (52.2%)	492 (52.8%)	399 (54.4%)
Abnormal, NCS	731 (46.2%)	422 (45.3%)	314 (42.8%)
Abnormal, CS	24 (1.5%)	17 (1.8%)	20 (2.7%)
Change from Baseline:			
No change	1,167 (75.8%)	724 (79.6%)	579 (81.3%)
Improved	154 (10.0%)	86 (9.5%)	68 (9.6%)
Worsened	219 (14.2%)	99 (10.9%)	65 (9.1%)
Missing	41	22	21

NCS: Not clinically significant. CS: Clinically significant.

Vital signs and clinical examination findings

Integrated safety analyses

Hypertension was reported in 2.2% of the overall silodosin safety population compared with 1.9% in the placebo population. Orthostatic hypotension was reported in 1.8% and 1.1% of the respective populations.

There were no clinically meaningful changes in supine SBP or DBP in the respective groups. Mean SBP fell by -2.5, -1.8, and -0.6 mm Hg and DBP fell by -1.4, -1.0 and -0.8 mm Hg in the respective groups. The mean changes in HR from baseline were 1.6, 1.7 and 1.6 bpm, respectively. Pre-dose positive tests were reported in 0.5% of the silodosin and placebo safety populations. Post-dose positive tests were reported in 2.0% and 0.5% of the respective populations.

For further details of issues with possible regulatory impact see Attachment 2 Section 8.5.

Postmarketing data

Silodosin has been launched under various trade names in multiple jurisdictions as follows:

2006: Japan in 2006

2009: US and Korea in 2009

2010: Lebanon, Germany, Ireland, Spain and France

2011: Portugal, Belgium, Romania, Italy, Greece, Netherlands, Czech Republic, Slovakia, Taiwan and Russia

2012: Cyprus, Bulgaria, Poland, Canada, Turkey and Ukraine

2013: Georgia, Belarus, Armenia, UAE, Croatia, China and Macau

The greatest single exposure has occurred in Japan with cumulative exposure to silodosin 8 mg of more than 2 million patient years.

In the EU territories, adverse drug reactions (ADRs) have been collected and recorded in the Periodic Safety Update Report (PSUR) No: 8 and the EU Summary of Product Characteristics (SmPC) (Table 8).

Table 8: Most common post-marketing ADRs in EU territories

System Organ Class/ MedDRA PT	Serious	Total (serious + non serious)	Included in EU SmPC
Psychiatric disorders			
Libido decreased	1	12	Yes (uncommon)
Nervous System disorder			
Dizziness	4	63	Yes (common)
Headache	2	29	No
Syncope	10	17	Yes (rare)
Ear and labyrinth disorders			
Vertigo	4	14	No (dizziness)
Vascular disorders			
Hypotension	6	10	Yes (uncommon)
Orthostatic hypotension	17	43	Yes (common)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	2	11	No
Nasal congestion	2	32	Yes (common)
Gastrointestinal disorders			
Abdominal pain	0	15	No
Diarrhoea	2	34	Yes (common)
Dry mouth	2	15	Yes (uncommon)
Nausea	3	27	Yes (uncommon)
Skin and subcutaneous tissue disorders			
Pruritus	1	10	Yes (uncommon)
Rash	3	11	Yes (uncommon)
Reproductive system and breast disorders			
Ejaculation disorder	2	22	Yes
Ejaculation failure	3	75	Yes (Anejaculation) (very common)
Erectile dysfunction	3	38	Yes (uncommon)
Retrograde ejaculation	8	74	Yes (very common)
Testicular pain	0	12	No
General disorders and administrative site conditions			
Drug ineffective	0	23	No
Fatigue	2	16	No
Malaise	15	29	No

Worldwide post-marketing safety data have been collected by Kissei and included in the PSUR No: 18 (Table 9). The pattern of post-marketing ADRs is comparable to that reported in clinical trials. However, new spontaneous and clinical trial reports have led to voluntary updates of national labels in Japan, US, EU and Canada. These include hypersensitivity/allergic reactions; abnormal liver function tests (LFTs); syncope; hypotension following co-administration with phosphodiesterase (PDE)-5 inhibitors; tachycardia and palpitations; stomatitis; gynaecomastia; and skin drug eruptions. Based on the clinical trial and post-marketing data, approximate estimates of frequency have been calculated for: orthostatic hypotension (1%), syncope (<0.1%), tachycardia (0.1%), hypersensitivity reactions (0.1%) and abnormal LFTs (0.1%).

Table 9: Most common post-marketing ADRs worldwide

MedDRA SOC	MedDRA PT (ver. 17.1)	Cumulative (incl. solicited) (IBD – 30 January 2015)	
		Serious	Total
Cardiac disorders	Palpitations	1	57
Eye disorders	Vision blurred	0	65
Gastrointestinal disorders	Abdominal discomfort	1	90
	Abdominal pain	1	54
	Abdominal pain upper	1	40
	Constipation	2	80
	Diarrhoea	11	803
	Dry mouth	2	54
	Dyspepsia	0	38
	Faeces soft	0	261
	Nausea	7	107
	Vomiting	2	31
General disorders and administration site conditions	Asthenia	3	44
	Death	37	37
	Fatigue	3	63
	Feeling abnormal	2	31
	Malaise	18	84
	Oedema peripheral	1	44
	Thirst	0	256
Hepatobiliary disorders	Hepatic function abnormal	11	43
Injury, poisoning and procedural complications	Floppy iris syndrome	3	31
Investigations	Blood pressure decreased	8	73
	Blood pressure increased	5	45
Musculoskeletal and connective tissue disorders	Back pain	1	31
Nervous system disorders	Dizziness	23	752
	Dizziness postural	4	186
	Headache	5	179
	Hypoaesthesia	1	34
	Loss of consciousness	47	68
	Somnolence	1	65
	Syncope	34	55

Intra-operative floppy iris syndrome (IFIS) during cataract surgery or glaucoma has been identified as an adverse reaction associated with α1a-blockers following reports in patients receiving tamsulosin.[15] In patients receiving tamsulosin, the risk of IFIS ranges from 43% to 90%, although the risk appears to be lower in patients receiving terazosin or doxazosin. A single case in a patient receiving silodosin was identified in the Phase II/III studies and a further 31 cases (three serious) have been identified post-approval. No estimate of the frequency of IFIS in patients treated with silodosin has been provided (see Clinical Questions in Attachment 2).

No new safety data have been reported in populations which have not been studied in clinical trials. These include patients aged >75 years, patients with severe hepatic or renal impairment, patients with mild symptoms of BPH and patients receiving 5-ARIs. Additional data will become available from several post-marketing surveillance studies which are on-going worldwide.

[15] Chang D, et al. Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg 2005; 31:664

Evaluator's conclusions on safety

Silodosin was generally well tolerated in the clinical trial program. The most common ADR identified in the overall safety population was retrograde ejaculation (23.6%), assumed to be drug related as it occurred in < 1% of the placebo population. Other ejaculatory disorders were less common but they also occurred more commonly in patients receiving silodosin. Loss of libido and erectile dysfunction were infrequent and less obviously causally related given the age of the patient population. Retrograde ejaculation was tolerated by most patients but it was reversible in those who withdrew from treatment. Retrograde ejaculation is likely to reduce fertility temporarily. However, this should be reversible when treatment is withdrawn. In the Phase II/III studies (including the extension studies), only 3.9% of patients withdrew due to retrograde ejaculation. Moreover, treatment compliance rates were consistently > 90% across studies. In the EU study with an active comparator, retrograde ejaculation was reported in 14.2%, 2.1% and 1.1% of the silodosin, tamsulosin and placebo groups. As the efficacy of silodosin and tamsulosin was comparable, there is no obvious explanation for the large difference in the rates of retrograde ejaculation between the groups (see Clinical Questions Attachment 2).

Other less common ADRs in the overall silodosin (n=1,581) and placebo (n=733) populations were dizziness (2.1% versus 0.8%), orthostatic hypotension (1.3% versus 1.0%), nasal congestion (1.3%), headache (1.3% versus 1.2%), diarrhoea (1.0% versus 0.3%), erectile dysfunction (0.9% versus 0.4%), rhinitis (0.8% versus 0.3%), libido decreased (0.8% versus 0.0%) and dry mouth (0.7% versus 0.3%). Most AEs were mild to moderate in intensity. There were seven deaths in the Phase II/III studies but none were considered drug related. Only four serious AEs (SAEs) were considered possibly related to silodosin (one case each of syncope, prostatic carcinoma, atrial arrhythmia and myocardial infarction). No significant safety signals relating to clinical chemistry, ECGs or vital signs were identified.

There were trivial falls in mean supine BP and the rate of orthostatic hypotension was low (predicted because of the high specificity of silodosin for the α1a-receptor). In the overall safety analysis, there were only two cases of syncope (0.08%) and one case each of pre-syncope and loss of consciousness (each 0.04%). The overall incidences of dizziness and postural dizziness were 2.03% and 0.04%, respectively. Tachycardia and palpitations were reported in 0.15% and 0.08% of patients, assumed to be reflex responses to blood pressure lowering.

The proposed Australian PI includes post-marketing safety updates relating to uncommon or rare ADRs including tachycardia and palpitations, abnormal LFTs, allergic reactions, syncope, skin rashes and drug eruptions and hypotension. IFIS is a well understood ADR which is highlighted in the proposed PI. In the overall safety analysis, there were only two reports of prostate cancer. Prostate cancer is a cause of LUTS and it should be excluded by ultrasound, rectal examination and/or prostate specific antigen (PSA) measurement before silodosin treatment is started. This is also highlighted in the proposed PI.

Retrograde ejaculation is an inconvenience which is reversible in patients who find it more distressing. Other ADRs are much less common and generally mild to moderate in severity. Potentially serious ADRs such as orthostatic hypotension and cardiac events are uncommon and reversible if treatment is withdrawn. Overall, the safety profile of silodosin is acceptable for the treatment of a non-life threatening condition.

First Round Benefit-Risk Assessment

First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Silodosin 8 mg daily provides a statistically significant improvement in LUTS associated with moderate to severe BPH. There are statistically significant improvements in QoL. There are improvements in urinary flow rate. The efficacy of silodosin 8 mg is comparable to tamsulosin 0.4 mg daily, another widely used α1a-blocker.The specificity of the α1a-blockers reduces the potential for supine and orthostatic hypotension. Silodosin acts quickly and efficacy is sustained for at least one year. Large Phase IV studies have confirmed the results of shorter term controlled studies. Silodosin is generally well tolerated and safe.	The improvement in symptoms in the controlled trials was substantial in patients treated with silodosin or placebo. There was a statistically significant difference in favour of silodosin but the difference compared with placebo was not clinically meaningful. Mean improvements in QoL were modest. Improvements in Qmax (the only objective efficacy measure) were generally minor and inconsistent between studies. Non-inferiority with tamsulosin was confirmed with a high degree of statistical significance. The safety profile of silodosin has been established with extensive post-marketing experience with several million patient/years of treatment. Uncertainties are outlined in the Risk Management Plan (RMP).

First round assessment of risks

Risks	Strengths and Uncertainties
Ejaculation disorders are very common. However, they are generally bothersome rather than a safety concern. They are reversible if therapy is withdrawn. Other ADRs are generally mild to moderate although there is the potential for uncommon serious ADRs (such as IFIS, syncope, hypersensitivity). Safety has not been established in sub-groups, including patients with severe renal or hepatic impairment and patients receiving concomitant 5α-Reductase inhibitors (5-ARIs).	Placebo- controlled studies confirm that retrograde ejaculation is an ADR, predicted by its pharmacological activity on the urinary tract. The safety profile of silodosin has been established by many years of post-marketing experience. These are addressed in the proposed PI and appropriate pharmacovigilance activities have been identified.

First round assessment of benefit-risk balance

The overall benefit-risk balance for the proposed indication is negative. The benefit-risk is positive in patients with severe LUTS but negative in patients with mild to moderate symptoms.

The pivotal and supportive studies have demonstrated clear statistically significant improvement in IPSS for silodosin compared with placebo in patients with moderate to severe symptoms associated with BPH. However, subjective improvements were not matched by significant objective improvements based on Qmax. The overall decrease in

IPSS was less than the 3 points required to demonstrate a minimum clinically meaningful benefit based on the AUA guideline. A borderline benefit was shown only in patients with severe symptoms (IPSS ≥ 20) in a post hoc analysis requested by the EMA. Clinically meaningful benefit in patients with mild or moderate LUTS has not been established.

The risk of mild to moderate ADRs is high although serious ADRs are uncommon. The most common ADR is retrograde ejaculation which occurs in approximately 25% of patients. However, this is reversible without sequelae when treatment is stopped. Less common ADRs include headache, dizziness and postural dizziness. IFIS, hypersensitivity and syncope are rare but serious ADRs. Most ADRs may be regarded as bothersome rather than serious but low tolerability may explain the relatively modest overall improvements in QoL. The pattern of ADRs and the associated risks are shared by other agents in the class and no specific ADRs related to silodosin have been identified. Risks associated with the pharmacology of silodosin including interactions, are shared by other agents in the class. No ADRs of concern have been identified in subgroups, including elderly patients aged ≥ 75 years. Almost all patients in the clinical trial program were either Caucasian or Japanese and controlled data are limited for other racial groups.

The safety and tolerability of silodosin has been established with extensive worldwide post-marketing experience. Risk has been quantified and the risk of unidentified ADRs is very low. However, risk in patients with severe hepatic or renal failure has not been fully evaluated in post-marketing surveillance data.

LUTS associated with BPH is a bothersome syndrome which affects quality of life. The use of silodosin may improve symptoms but there is no evidence that treatment ameliorates the underlying condition, improves long-term outcomes or reduces surgical intervention. The risks associated with silodosin are low and arguably acceptable in patients with severe symptoms. However, the risks do not outweigh benefit in patients with mild or moderate symptoms

First Round Recommendation Regarding Authorisation

Authorisation is not recommended for the proposed indication:

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult men.

1. The sponsor suggests that silodosin improves the signs of BPH but it is unclear what these signs are. There should be no implication that silodosin reduces prostate size.
2. A clinically meaningful benefit compared with placebo for mild to moderate symptoms of BPH has not been established.
3. The benefit-risk is not favourable in patients with mild to moderate symptoms.

However, subject to satisfactory responses to the Clinical questions (see Attachment 2) authorisation is recommended for the indication:

Relief of severe lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men (IPSS≥ 20).

Note: The FDA and EMA both approved the indication proposed by the sponsor based on statistically significant improvements in the signs and symptoms of BPH for silodosin compared with placebo. Clinically meaningful efficacy was accepted without question by the FDA but it was challenged by the EMA. In a post hoc analysis requested the EMA, only in patients with baseline IPSS ≥ 20 was a threshold for clinically meaningful improvement of three points achieved (see Clinical question 5 Attachment 2). The EMA also questioned

the study designs which biased the outcomes in favour of the active treatments compared with placebo.[16]

Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The second round assessment of benefits is positive following new data provided by the sponsor. The benefits in patients with IPSS < 20 are modest but comparable with other approved products in the class.

Second round assessment of risks

The second round assessment of risks is positive following arguments provided by the sponsor. The frequency of ADRs is high but comparable with other approved products in the class. Most ADRs are 'bothersome', reversible and not a risk to health.

Second round assessment of benefit-risk balance

The second round assessment of benefit-risk is positive.

Second round recommendation regarding authorisation

Authorisation is not recommended for the proposed indication:

Treatment of the signs and symptoms of benign prostatic hyperplasia in adult men

However, authorisation is recommended for the revised indication:

Relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men.

V. Pharmacovigilance findings

Risk management plan

Summary

· Mayne Pharma International Pty Ltd has submitted EU-RMP version 11.2, dated January 2015; data lock point (DLP) 30 January 2014 and ASA version 0.2, dated 23 December in support of this application.

[16] see CHMP Assessment Report for Urorec: EMA/793234/2009, 10 January 2010; and CDER/FDA: NDA 22-206, 10 October 2008

- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 10.

Table 10: Summary of safety concerns

[17]R=routine and A=additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Intraoperative Floppy Iris Syndrome (IFIS)	ü*	–	ü	ü
	Orthostatic hypotension/hypotension	ü	–	ü	–
	Syncope/loss of consciousness	ü	–	ü	–
	Hypersensitivity (including allergic type reactions, such as facial oedema, pharyngeal oedema and swollen tongue)	ü	–	ü	–
	Abnormal Liver Function Tests (LFTs)	ü*	–	ü	–
	Tachycardia	ü*	–	ü	–
	Palpitations	ü*	–	ü	–
	Abnormal ejaculation, erectile dysfunction	ü*	–	ü	–
Important potential risks	Use in moderate/severe renal impairment	ü*	–	ü	–
	Misdiagnosis of prostate cancer	ü*	–	ü	–
	Photosensitivity reactions	ü	–	–	–
	Genital discomfort/burning	ü	–	–	–
	Gynaecomastia, breast enlargement,	ü*	–	–	–

[17] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	breast tenderness				
	Use in patients with pre-existing cardiovascular disease	ü*	–	ü	–
	Concomitant treatment with strong CYP 3A4 inhibitors	ü	–	ü	–
	Concomitant use with other α-blockers	ü	–	ü	–
	Concomitant treatment with phosphodiesterase type 5 inhibitors	ü	–	ü	–
	Concomitant use with antihypertensive medicines	ü	–	ü	–
Missing information	Use in severe hepatic impairment	ü	–	ü	–
	Use in patients with a serum creatinine >2.0 mg/dL	ü	–	ü	–
	Concomitant use of 5- α -reductase inhibitors	ü	–		–
	Patients aged ≥ 75 years	ü	–	ü	–

Targeted questionnaires used for follow up

- Routine pharmacovigilance activities only are proposed
- Additional risk minimisation is proposed for the important identified risk: IFIS
  - Dear Health Care Professional letter (and educational materials) for eye surgeons

Conclusions and wording for conditions of registration
The recommendations made in the first round evaluation report have been addressed by the sponsor. There are no new or outstanding recommendations.

The evaluator has no objection to the implementation of the Urorec Risk Management Plan.

The suggested wording is:

- Implement Urorec EU-RMP version 11.2, dated January 2015; DLP 30 January 2014 with ASA version 0.2, dated 23 December 2016, submitted with application PM-2016-00744-1-3, and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has recommended approval based on the chemistry and quality aspects of the submission with the exception of the outstanding issues outlined below.

The following were noted:

- Silodosin is considered to be BCS class 3 (high solubility, low permeability). It is a white to pale yellowish white powder. It has pH dependent solubility and is not considered to be hygroscopic.
- Silodosin contains one chiral centre and is used as the R-enantiomer.
- The capsule manufacturing process uses standard processes such as mixing, wet granulation, sieving, drying, blending, encapsulation and packaging. The process has been validated and in-process controls are adequate for the dose form.
- The excipients are conventional and include: mannitol, pregelatinised maize starch, sodium lauryl sulphate and magnesium stearate.
- The hard capsules are packed in blisters, in cartons containing 10 capsules (starter packs) and 30 capsules.
- The stability data provided supports a shelf life of 36 months when stored below 25°C (stored in the original package to protect from light and moisture).

There are outstanding GMP clearances that will need to be provided prior to registration.

Nonclinical

The nonclinical evaluator had no nonclinical objection to the registration of silodosin.

A summary of the findings of the nonclinical evaluation is as follows:

- Primary pharmacology studies adequately support the proposed use of silodosin for the treatment of BPH.
- Silodosin displayed moderate off-target affinity for 5-HT1A, 1B, 1D and 7, β2 and dopaminergic D3 receptors. Specialised safety pharmacology studies did not identify any clinically significant hazards.
- Silodosin metabolism is dependent on CYP 3A4, alcohol and aldehyde dehydrogenase and UGT 2B7. As well, silodosin is a substrate of P-gp. Drugs that affect P-gp and these enzymes may affect the clearance of silodosin.
- The key target organs for toxicities were the liver, the gastrointestinal tract and the reproductive organs. Effects on the liver and reproductive organs are likely rodent-specific response to the pharmacological actions of silodosin although post-marketing data have identified incidences of hepatobiliary disorders. Irritation in the gastrointestinal tract occurred at higher doses than those expected with clinical use.
- Silodosin was not genotoxic. Carcinogenicity studies indicated that tumour development (mammary tumours in mice, thyroid tumours in rats) was secondary to rodent-specific hormonal disturbances induced by silodosin.
- The sponsor's proposed Pregnancy Category of B3 is considered appropriate for silodosin.

Clinical

The clinical evaluator recommended rejection for the originally proposed indication '*Treatment of the signs and symptoms of benign prostatic hyperplasia in adult men'*. However, recommended approval for the revised indication '*Relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men'*.

The clinical evaluator was primarily concerned about:

- The modest size and clinical relevance of the change from baseline in total IPSS score (approximately 2 to 3 points versus placebo) and Qmax (approximately 2 to 3 mL/sec for silodosin versus approximately 1 to 2 mL/sec for placebo)

The pharmacology studies noted the following pharmacokinetic findings:

- The absolute bioavailability of 4mg oral silodosin is approximately 32%.
- C_{max} and AUC_{0-24} of silodosin increased in a dose-proportional manner from 4 mg to 8 mg following single or 7 daily oral doses (proposed formulation) and from 0.1 mg to 16 mg using the Method A formulation.
- Following seven daily doses of 4 mg (1 x 4 mg capsule) or 8 mg (2 x 4 mg capsules) silodosin the C_{max}, and AUC were dose-proportional, whereas, there was little difference between the T_{max}, $t_{1/2}$ and Kel values following doses of either strength.
- Steady-state conditions appeared to be achieved following 3 days of dosing with silodosin.
- Mean T_{max} values ranged from 2.3 to 2.6 h after single or multiple 4 mg or 8 mg oral doses.
- Food delays the T_{max} (2.09 versus 1.36 hrs), and decreases the C_{max}, by approximately 30% but has little effect on the AUC_{0-48h} (approximately 7% lower) following a single 4mg oral dose of silodosin.
- The mean C_{max}, and AUC_{0-24h} of 8 mg silodosin taken after breakfast for 7 days were 62 ng/mL and 373 h.ng/mL, respectively in US patients aged 45 to 70 years, and 87 ng/mL and 433 h.ng/mL in German patients aged 45 to 64 years.
- Silodosin has a steady state volume of distribution of 49.5 L and a total body clearance of 167 mL/min
- Mean CL total/F and Vdss/F values were 792 mL/min and 264 L, respectively in healthy subjects following a single oral 4mg dose. These values decreased to 251 mL/min and 155 L, respectively, in subjects with renal impairment (creatinine clearance (CLCR) values of 11-50 mL/min).
- In patients with BPH there was no silodosin accumulation following multiple-doses. In the target population the estimated mean CL and Vd were 0.302 L/h/kg and 2.24 L/kg, respectively.
- Relative to subjects with normal renal function, the C_{max}, and AUC for unbound silodosin increased by approximately 1.6 fold and 1.7 fold respectively, in subjects with mild to moderate renal impairment. In subjects with severe renal impairment there was a 2.2 fold increase in C_{max}, and a 3.7 fold increase in AUC.
- Moderate hepatic dysfunction had a minimal effect on unbound silodosin PK (10 to 20% increases in C_{max}, and AUC, respectively).
- Plasma protein binding is approximately 95% (predominantly to α1-acid glycoprotein).
- Excretion occurs mainly through the faecal (55%) and urinary (33%) routes.

- PopPK modelling identified C-reactive protein, ALT, weight, age and creatinine as significant covariates for either silodosin clearance or volume of distribution.
- PK interactions were noted for the concomitant administration of silodosin and the moderate CYP3A4 inhibitor diltiazem (approximately 30% increase in silodosin AUC, delay in T_{max} of 1.25 h). Concurrent administration of ketoconazole (a strong CYP3A4 inhibitor) with silodosin resulted in a 3.1 fold increase in silodosin AUC and a 3.7 fold increase in C_{max}.

The pharmacology studies noted the following pharmacodynamic findings:

- In studies of Japanese patients at doses lower than proposed for the relief of LUTS associated with BPH (0.1 to 4mg twice daily), silodosin demonstrated dose dependent improvement in LUTS; however the differences observed were not statistically significant. Improvements were noted within 2 to 4 weeks of commencing treatment.
- Silodosin at 8 mg or 24 mg/day for 5 days had no meaningful effect on heart rate, PR, and QRS interval duration or on cardiac repolarisation.
- More subjects had positive orthostatic tests (Type I and II) after a single dose of silodosin (35% and 27%) than after placebo (14% and 9.5%). Positive orthostatic tests occurred at doses from 1 to 16 mg.
- PD interactions (positive orthostatic test) were minimal when silodosin was co-administered with a PDE-5 inhibitor (sildenafil 100mg or tadalafil 20 mg)
- Co-administration of silodosin with antihypertensives (metoprolol 50 mg, amlodipine 10 mg, Lisinopril 20 mg) was generally not associated with clinically significant orthostatic hypotension.

Efficacy

Study SI04009 (pivotal) was a Phase III, randomised, double-blind, placebo-controlled US study in 461 patients to assess the efficacy and safety of silodosin in the treatment of the signs and symptoms of BPH. Key inclusion criteria were age ≥ 50 years, bladder outlet obstruction, as defined by a Qmax between 4 and 15 mL/sec, with a minimum voided volume of ≥ 125 mL and an IPSS ≥ 13. Duration of disease was not considered. Key exclusion criteria were history of, or current, neurogenic bladder and other bladder conditions that might affect bladder function, history of significant postural hypotension, and history of inadequate clinical response to the use of α blockers specifically for the relief of BPH symptoms. Patients who were already on an α blocker had to have been washed out by 10 days prior to Visit 1 (4 weeks prior to randomisation), and 5 α-reductase inhibitors were excluded within 6 months of Visit 1. After a 4 week single-blind placebo run-in period, subjects were randomised to receive 8 mg silodosin (2 x 4 mg capsules) or matching placebo with food for 12 weeks. Subjects who had a marked placebo response during the run-in period (>30% decrease in IPSS or 3 mL/sec increase in Qmax) were discontinued.

Baseline demographic characteristics were similar for the two treatment groups. The majority of patients were Caucasian (87.6%), with a mean age of 64.2 years (range 44.9 to 88.1 years; with 88.7% < 75 years old). The baseline medical history of patients in the placebo and silodosin groups included: cardiovascular (55.7% versus 50.6%); hypertension (34.6% versus 30.9%) and impaired renal function (28.9% versus 33.5%).

The primary efficacy endpoint was change in IPSS from baseline to Week 12. The mean reduction from baseline in IPSS total score was -6.5 in the silodosin group and -3.6 in the placebo group. The difference compared with placebo was -2.8 (95% CI: -3.9, -1.7, p<0.001). A statistically significant reduction was seen as early as Week 0.5/1 and was

sustained through to Week 12. Patients also showed improvement in both the irritative and obstructive subgroups of the IPSS, in urinary flow rate (Qmax), and in IPSS QoL.

Study SI04010 (pivotal) was a US study and had an identical design to Study SI04009. It was conducted in 462 patients to assess the efficacy and safety of silodosin in the treatment of the signs and symptoms of BPH. After a 4 week placebo run-in, patients received 8 mg silodosin (2 x 4mg capsules) or matching placebo with food for 12 weeks. Subjects who had a marked placebo response during the run-in period (>30% decrease in IPSS, or 3 mL/sec increase in Qmax) were discontinued. Baseline demographic characteristics were similar for the two treatment groups. The majority of patients were Caucasian (90.9%), with a mean age of 65.1 years (range 50.8 to 86.8 years; with 86.4% < 75 years old). The baseline medical history of patients in the placebo and silodosin groups included: cardiovascular (56.8% versus 58.4%); hypertension (33.2% versus 32.2%) and impaired renal function (33.6% versus 33.9%).

The primary efficacy endpoint was change in IPSS from baseline to Week 12. The mean reduction from baseline in IPSS total score was -6.3 in the silodosin group and -3.4 in the placebo group. The difference compared with placebo was -2.9 (95% CI: -4.0, -1.8, p<0.001). A statistically significant reduction was seen as early as Week 0.5 / 1 and was sustained through to Week 12. Patients also showed improvement in both the irritative and obstructive subgroups of the IPSS, in urinary flow rate (Qmax) and in IPSS QoL.

Study KMD3213-IT-CL-0215 (pivotal) was a Phase III, randomised, double-blind, international study in 955 patients with moderate to severe symptomatic BPH comparing the efficacy and safety of silodosin, tamsulosin and placebo in the treatment of the signs and symptoms of BPH. Key inclusion and exclusion criteria were similar to Studies SI04009 and SI04010. After a 4 week single-blind placebo run-in period, patients received 8 mg silodosin (1 x 8 mg capsule) or 0.4 mg tamsulosin or matching placebo with food for 12 weeks. Patients who had a marked placebo response during the run-in period (≥ 25% decrease in IPSS) were discontinued. Baseline demographic characteristics were similar for the 3 treatment groups. All patients were Caucasian, with a mean age of 65.8 years (range 50 – 87 years; with 87.3% < 75 years old). Overall, 345 out of 955 subjects (36.1%) had received some treatment for BPH in the past, with similar percentages of subjects in the 3 treatment groups. The baseline medical history of patients in the placebo, silodosin, and tamsulosin groups included: cardiovascular (51.6% versus 59.6% versus 55.2%); and hypertension (38.9% versus 47.5% versus 44.0%).

The primary efficacy endpoint was change in IPSS from baseline to Week 12. The mean reduction from baseline in IPSS total score was -7.0 in the silodosin group, -6.7 in the tamsulosin group, and -4.7 in the placebo group. The adjusted mean differences compared with placebo were -2.3 (95% CI: -3.2, -1.4, p<0.001) for silodosin and -2.0 (95% CI: -2.9, -1.1, p<0.001) for tamsulosin. A statistically significant reduction (silodosin versus placebo) was seen as early as Week 1 and was sustained through to Week 12. The treatment difference between silodosin and tamsulosin was 0.3 (95% CI: -0.4, 1.0) (non-inferior based on the pre-defined limit. Non-inferiority of silodosin was concluded if the lower limit of the CI was ≥ -1.5). Patients receiving silodosin also showed improvement in both the irritative and obstructive subgroups of the IPSS, in urinary flow rate (Qmax), and in IPSS QoL.

Study SI0411 (supportive): this was a Phase III, open-label extension study in patients with BPH who had previously participated in SI04009 and SI04010 to investigate the sustained efficacy and safety of silodosin 8 mg for an additional 40 weeks. In total 435 of 661 (65.8%) patients completed the study, with 151 patients (23.9%) discontinuing due to AEs or lack of efficacy. At Week 40, there was a mean decrease in IPSS total score of -3.1 (-4.4 in patients previously given placebo; and -1.6 in patients previously given silodosin).

Study IT-CL-0215 (supportive): this was a Phase III, open-label extension study in patients with BPH who had previously participated in IT-CL-0215 to investigate the sustained efficacy and safety of silodosin 8 mg for an additional 40 weeks. In total 444 of 500 (88.8%) completed the open-label extension phase of the study, with 28 patients (5.6%) discontinuing due to AEs or lack of efficacy. In patients who previously received silodosin or tamsulosin, the mean IPSS decreased slightly at the start of the OL phase (silodosin -0.82; tamsulosin -0.83) and this was maintained for the rest of the treatment period. In patients previously randomised to placebo there was an immediate fall in mean IPSS (-2.68) which was sustained at Week 26 (-2.68) and Week 52 (-3.01). A similar pattern of response was seen for the irritative and obstructive subscores of the IPSS. All 3 groups showed further improvement in QoL but little change in Qmax.

Study KMD-3213-US021-99 (supportive) was a pilot Phase II, placebo-controlled, double-blind, dose-adjustment study of the safety, efficacy and tolerability of silodosin (4 mg or 8 mg) given for 8 weeks to patients with BPH. The mean reduction from baseline in IPSS total score was -6.8 in the silodosin 8 mg group, -5.7 in the silodosin 4 mg group, and -4.0 in the placebo group. Compared with placebo, these reductions were statistically significant in both the 8 mg (p=0.0018) and 4 mg (p=0.0355) silodosin groups. The difference between the two silodosin groups was not statistically different (p=0.2871).

Study KMD-3213-IT-CL-0376 (supportive) was a 24 week Phase IV, open label, single-arm study of silodosin 8 mg in 994 patients with signs and symptoms of BPH. The primary endpoint was the percentage of treatment responders at study end (defined as a decrease ≥ 25% in the IPSS total score). A total of 77.1% of patients were treatment responders, with a mean change in IPSS of -8.3.

Study KMD-305 (supportive) was a Phase III, open-label study of efficacy and safety of silodosin (4mg bd, which could be down-titrated to 2mg bd) in 361 Japanese patients with moderate to severe symptoms of BPH (IPSS ≥ 8). Mean IPSS scores fell from 18.4 at baseline to 13.1, 10.6 and 8.2 at Weeks 4, 12 and 52, respectively. Mean Qmax increased from 9.51 mL/sec at baseline to 11.35, 10.57 and 12.36 mL/sec at Weeks 4, 12 and 52, respectively.

Study KMD-304 (supportive) was a 12 week, double blind, parallel group, active and placebo controlled study comparing the efficacy and safety of silodosin 8 mg, tamsulosin 0.4 mg and placebo (randomised 2:2:1) in 457 Japanese patients with moderate to severe micturition disorder associated with BPH (IPSS ≥ 8). The mean changes from baseline to completion in IPSS were -8.3 in the silodosin 8 mg group, -6.8 in the tamsulosin 0.4 mg group, and -5.3 in the placebo group.

Safety

The overall pooled safety analysis for silodosin 8 mg includes Phase II-IV studies: KMD3213-US-021-99, SI04009, SI04010 and KMD3213-IT-CL 0215 (both double blind and open label phases), SI04011 for the open label phase and KMD3213-IT-CL-0376. In total, 2,617 patients had a mean silodosin exposure of 202.2 days, with 66.9% of patients having at least 6 months exposure, and 15.0% having ≥ 12 months exposure. The majority of patients were Caucasian (96.6%), and the median age was 66 years (range 44 to 87). At baseline, the IPSS score was moderate (8-19) in 55.7% of patients and severe (20-35) in 40.2% of patients. The most frequent concomitant diseases were: cardiovascular disease (56.3%), hypertension (41.3%) and diabetes (10.6%).

In the silodosin 8 mg (N= 931) versus placebo (N= 733) safety population, mean silodosin exposure was 77.8 days, with 64.9% having at least 12 weeks exposure. Demographic characteristics were similar to the overall population, although more patients had a severe IPSS score at baseline (51.7%) and fewer had hypertension (30.7%). Unless otherwise

specified, results are presented for the overall pooled safety analysis population. The pooled results reflect the results of the individual studies.

Treatment-emergent AEs (TEAEs) were experienced by 48.3% of patients in the overall population. The most common TEAEs were retrograde ejaculation (14.3%), ejaculation failure (7.2%), diarrhoea (2.7%), dizziness (2.6%), nasopharyngitis (2.1%) and headache (2.1%). The most common adverse drug reactions were similar to the TEAEs: retrograde ejaculation (14.3%), ejaculation failure (7.1%) and dizziness (2.0%). In the silodosin versus placebo safety population the most common ADRs occurring at a greater frequency than placebo were retrograde ejaculation (21.5% with silodosin versus 0.8% with placebo), dizziness (1.8% versus 0.8%), orthostatic hypotension (1.2% versus 1.0%), nasal congestion (1.0% versus 0.1%), erectile dysfunction (0.6% versus 0.4%) and diarrhoea (0.6% versus 0.3%).

A total of 91 patients had 120 serious TEAEs. Of these, 79 patients on silodosin 8 mg had 103 serious TEAEs, 4 patients on tamsulosin 0.4 mg had 7 serious TEAEs and 8 patients on placebo had 10 serious TEAEs. The majority of serious TEAEs in any treatment group were considered unrelated to study treatment, were of moderate to severe intensity and generally resolved without sequelae. Cases considered as possibly related to silodosin included syncope, prostate cancer, atrial arrhythmia, myocardial infarction, bradycardia, transient ischaemic attack (TIA), cerebral ischaemia, sudden hearing loss and dizziness. One patient developed IFIS following eye surgery (a further 31 cases (three serious) have been identified post-approval).

In total, 225 (8.60%) patients had a TEAE leading to permanent study discontinuation. The most common TEAEs were: retrograde ejaculation (2.4%), ejaculation failure (1.0%), dizziness (0.5%), erectile dysfunction (0.4%) and diarrhoea (0.4%). In the silodosin versus placebo safety population discontinuations were more common in patients on silodosin (4.3%) than in patients on placebo (1.9%) with the difference largely due to retrograde ejaculation (1.9% versus 0.0%). Orthostatic hypotension was a cause of discontinuation in only 2 patients on silodosin (0.2%), as compared to 1 patient with placebo (0.1%).

Seven deaths occurred: 5 on silodosin (myocardial infarction, cardiopulmonary arrest, squamous cell carcinoma (SCC) lung, road traffic accident and cardiac failure associated with concomitant disease), and one each on tamsulosin (multiple carcinomas) and placebo (hypertensive cerebral haemorrhage); none were considered related to treatment.

No clinically meaningful changes or trends in liver function, renal function or haematological parameters were noted. In the silodosin versus placebo safety population, PSA worsened during treatment in 4.1% and 3.9%, and glycosylated haemoglobin (HbA1c) worsened in 6.3% and 4.0% of the silodosin and placebo groups, respectively. There were no meaningful changes in T3, T4 or TSH, or differences from placebo in the clinical studies.

Risk management plan

The TGA has accepted the EU-RMP (Version 11.2, dated January 2015; DLP 30 January 2014) with an updated ASA (Version 0.2, dated December 23 2016). There were no outstanding issues.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are shown in Table above.

Risk-benefit analysis

Delegate's considerations

Quality

The quality evaluator has no objections to approval from a chemistry and quality perspective. There are outstanding GMP clearances that will need to be provided prior to registration.

Nonclinical

The nonclinical evaluator had no objections to the registration of silodosin.

Efficacy

The three pivotal 12 week studies (2 in the US, 1 in Europe) demonstrated the efficacy of silodosin 8 mg in 1,878 patients with signs and symptoms of BPH as measured by IPSS. The results were consistent, with decreases in IPSS total score of -6.3 to -7.0 in the silodosin groups of the pivotal studies and -6.7 in the tamsulosin group in the EU study. Changes in the placebo groups ranged from -3.4 to -4.7. While the differences compared with the active treatment groups were statistically significant (range -2.3 to -2.9, $p<0.0001$), they are modest from a clinical perspective (but consistent with the findings for Flomaxtra). In the EU study there was also statistical evidence for non-inferiority of silodosin compared with tamsulosin based on the pre-defined lower limit of the CI being ≥ -1.5 (actual result -0.4). This non-inferiority margin is appropriate based on clinically relevant differences in IPSS deemed to be in the range of 2 to 3. Analyses for the secondary endpoints were consistent with those for the primary endpoint. Supportive evidence is provided by 2 long term extension studies in 1,161 patients, demonstrating maintenance of effect for 1 year. The baseline demographic and disease related characteristics of patients in the Phase III trials are similar to those in the anticipated Australian patient cohort.

A significant weakness in the studies was the exclusion of placebo responders from randomisation. The sponsor was asked by the EMA to justify this step which enriched the study population in favour of active treatment. Post hoc analyses of the EU and US studies showed that this did not influence the overall conclusions of the controlled studies.

Safety

The safety profile for silodosin 8 mg was demonstrated in 1,664 patients with LUTS/BPS in the silodosin versus placebo safety population and 2,617 patients in the Phase II-IV studies. ADRs include retrograde ejaculation, dizziness, orthostatic hypotension, nasal congestion, erectile dysfunction and diarrhoea. Overall, a higher incidence of ADRs was observed in silodosin treatment groups, largely due to the increase in retrograde ejaculation.

In the only active comparator study, a higher incidence of ADRs was seen on silodosin (21.5%) compared with tamsulosin (10.4%). Again, this was largely due to retrograde ejaculation (14.2% versus 2.1%). Retrograde ejaculation was tolerated by most patients and it was reversible in those who withdrew from treatment. Overall, there was a low incidence of orthostatic hypotension and dizziness. One case of IFIS following eye surgery was reported in the clinical trial program and a further 31 cases (three serious) have been identified post-approval. This is likely a class effect, and several studies suggest that IFIS is more likely to occur with the selective α blockers compared to the other non-selective α blockers.

Indications

In the response to Question 7 of the Clinical questions (Attachment 2), the sponsor proposed the revised indication '*Relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia in adult men*. This is generally consistent with the approved indication for the similar product (Flomaxtra) with the exception of the specification of use '*in adult men'*.

Dose

The 8 mg dose of silodosin was based on multiple pre-clinical and clinical pharmacology studies. In the dose finding Study US021-99, efficacy was marginally superior in the 8 mg group compared with 4 mg group, while safety and tolerability were comparable for the two doses. The data support the use of the 8 mg dose with the option to reduce the dose to 4 mg if necessary.

Data deficiencies

There is limited experience with silodosin in patients with BPH and moderate or severe renal impairment or in patients with abnormal liver function tests.

Conditions of registration

The following are proposed as conditions of registration and the sponsor is invited to comment on this:

- The implementation in Australia of the EU Risk Management Plan for Urorec (silodosin) (Version 11.2, dated January 2015; DLP 30 January 2014) with Australian Specific Annex (Version 0.2, dated December 23 2016) and any future updates as agreed with the TGA.

Summary of Issues

The efficacy of silodosin in BPH has been demonstrated using the subjective International Prostate Symptom Score (IPSS) as the primary efficacy variable. Only a modest change in total IPSS score (approximately 2 to 3 points) has been demonstrated and the clinical relevance of this change is queried. Qmax was a secondary outcome and the only objective measure in the pivotal studies, and again, only a modest benefit was observed.

Proposed action

The Delegate had no reason to say, at this time, that the application for Urorec should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issue:

1. Does the committee agree that a modest change in total IPSS score (approximately 2 to 3 points) and Qmax (approximately 2 to 3 mL/sec) is clinically relevant and sufficient evidence of efficacy to support potential long-term use of silodosin?
2. Does the committee consider that the sponsors risk minimisation strategy for IFIS is adequate?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor

1. The proposed statement in the Distribution subsection of the PI states a volume of distribution of 0.81 L/kg, which is consistent with the EU SmPC. However in the US label it states an apparent volume of distribution of 49.5 L. Can you please clarify from which clinical trials these data are derived and why one is selected over the other?
2. A number of changes have been made to the Clinical Trials section of the PI that is not included in the current EU SmPC, although it is noted some of the results are included in the US label. In particular, addition of the IPSS quality of life results, Qmax results, and a statement about comparable results in subgroups based on age and race. Please advise whether these changes have previously been, or will be, proposed for the EU SmPC.

Response from Sponsor

Response to Delegate's questions

TGA question

The proposed statement in the Distribution subsection of the PI states a volume of distribution of 0.81 L/kg, which is consistent with the EU SmPC. However, in the US label it states an apparent volume of distribution of 49.5 L. Can you please clarify from which clinical trials these data are derived and why one is selected over the other?

Response to question

The volume of distribution was assessed in the Study KMD-308 after a single IV administration of a 2 mg of silodosin over a 4 h infusion in healthy adult males. The volume of distribution resulted 49.5 L, therefore after correction of the total volume by the mean weight of the subjects (61.02 Kg) it results in a value of 0.81 L/kg. In conclusion, the two values are equivalent; the only difference is the unit of measure.

TGA question

A number of changes have been made to the Clinical Trials section of the PI that is not included in the current EU SmPC, although it is noted some of the results are included in the US label. In particular, addition of the IPSS quality of life results, Q_{max} results, and a statement about comparable results in subgroups based on age and race. Please advise whether these changes have previously been, or will be, proposed for the EU SmPC.

Response to question

The changes made to the Clinical Trials section of the PI are based on data already provided to EMA. This data was assessed by EMA before the approval of the current EU SmPC. With reference to the Renal function expressed in terms of estimated glomerular filtration rate (eGFR) and chronic kidney disease stages, it will be proposed also for the EU SmPC.

Advisory Committee Considerations

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Urorec hard gelatine capsules containing 4 mg and 8 mg of silodosin to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) in adult men.*

In making this recommendation the ACM:

- noted that there was a preference for sponsor included eGFR but had not included stages of chronic kidney disease when describing renal function in the PI.
- expressed concern with post-operative risks of IFIS

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

A statement in the Precautions section of the PI and relevant sections of the CMI to more accurately reflect the product including:

> *IFIS (a variant of small pupil syndrome) has been observed during cataract surgery in a significant portion of ~~some~~ patients on α1-blockers or previously treated with α1-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. ~~Discontinuing treatment with an α1-blocker 1-2 weeks prior to cataract surgery has been recommended.~~ 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 been treated with silodosin, in order to ensure appropriate measures are in place to minimise the effects of peri-operative IFIS.'*

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Does the committee agree that a modest change in total IPSS score (approximately 2 to 3 points) and Qmax (approximately 2 to 3 mL/sec) is clinically relevant and sufficient evidence of efficacy to support potential long-term use of silodosin?*

The ACM agree that a modest change in total IPSS score and Qmax is clinically relevant and sufficient evidence of efficacy to support potential long-term use of silodosin.

2. *Does the committee consider that the sponsors risk minimisation strategy for IFIS is adequate?*

The ACM advised that the sponsors risk minimisation strategy for IFIS is adequate provided that the sponsor include the suggested PI and CMI changes. ACM noted that the ongoing risk would need to be considered for silodosin, as well as including single and combination medication for other alfa blockers.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Urorec silodosin 8 mg hard capsule blister pack and Urorec silodosin 4 mg hard capsule blister pack for the following indications:

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

Specific conditions of registration applying to these goods

The silodosin EU-Risk Management Plan (EU-RMP), version 11.2, dated January 2015; DLP 30 January 2014) with Australian Specific Annex (Version 0.2, dated December 23 2016, included with submission PM-2016-00744-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Urorec approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au