European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Urorec

International Nonproprietary Name: silodosin

Procedure No. EMEA/H/C/001092

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@ema.europa.eu http://www.ema.europa.eu

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Recordati Ireland Ltd. submitted on 30 October 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Urorec, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 21 February 2008.

The legal basis for this application refers to:
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The applicant applied for the following indication: "Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)."

Information on Paediatric requirements
Pursuant to Article 7, the application included an EMEA letter dated 31st July 2008 on the applicability of the EMEA decision dated 21st April 2008 on a class waiver on conditions, granted for products intended to treat:

- *Benign prostatic hyperplasia*

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
Urorec has been given a Marketing Authorisation in Japan on 23/01/06, South Korea on 23/04/08 and USA on 08/10/08.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: Robert James Hemmings Co-Rapporteur: Antonio Addis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 30 October 2008.
- The procedure started on 19 November 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 February 2009.
- During the meeting on 16-19 March 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 March 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 19 October 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 2 November 2009.

- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Urorec on 19 November 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 November 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

BPH is a non-malignant enlargement of the prostate due to cellular hyperplasia of both glandular and stromal elements. As the prostate increases in size it may exert pressure on the lumen of the prostatic urethra, resulting in a gradual obstruction to urine flow. The manifestation and severity of the disease vary and BPH does not always progress to cause lower urinary tract symptoms (LUTS). Studies have shown that urinary flow rate and prostate size usually do not correlate with the severity and number of symptoms, which vary from subject to subject. The prevalence of BPH increases with age, especially after the fifth decade. On the basis of autopsy studies, BPH prevalence is 8% in men aged 31 to 40 years, 40 to 50% in men aged 51 to 60 years and >80% in men aged >80 years. In subjects with LUTS suggestive of BPH, both an obstructive and a storage component contribute to the symptoms and impairment of outflow. The obstructive component relates primarily to the increased size of the prostate, and the storage component relates to the tone of the smooth muscle in the prostatic capsule and stroma. The aim of therapy is to improve LUTS and quality of life (QOL) and to prevent complications, such as urinary retention or upper urinary tract dilatation. Initial management of men with LUTS can be categorised into 1) watchful waiting, 2) medical therapy, and 3) surgical treatment. Medical therapy may consist of the use of 5 α-reductase inhibitors (finasteride, dutasteride) or α-adrenoreceptor antagonists (terazosin, doxazosin, tamsulosin, prazosin, alfuzosin).

The active substance of Urorec is silodosin. Silodosin is an α1-adrenoreceptor antagonist that selectively affects the prostate, the urethra, and the trigone of the urinary bladder in the lower urinary tract as a therapeutic agent for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

This application is made via a centralised procedure according to Regulation (EC) No 726/2004 Article 3(2)(a), i.e. new active substance. The application is submitted in accordance with the Article 8(3) in Directive 2001/83/EC, i.e. new active substance, full dossier. The initial indication at the submission was: “Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)”.

No formal scientific advice had been given by the CHMP. No regulatory guidance on the investigation of products for the treatment of signs and symptoms of BPH is available.

The claimed indication was: “Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)”.

The approved indication is: “Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)”. The recommended dose is one capsule of Urorec 8 mg daily. For special patient populations, one capsule of Urorec 4 mg daily is recommended.

There is no paediatric development programme for silodosin. A class waiver on conditions, granted for products intended to treat benign prostatic hyperplasia has been issued by the EMEA.

2.2 Quality aspects

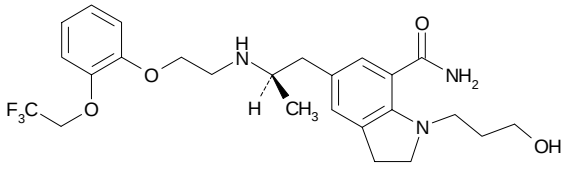
Introduction

Urorec is presented in the form of hard capsules containing 4 mg and 8 mg of silodosin as active substance. The other ingredients are mannitol, pregelatinised starch, purified water, sodium lauril sulfate and magnesium stearate. Other ingredients of the capsule shell are gelatine, titanium dioxide and colourants.

The hard capsules are marketed in polyvinylchloride (PVC)/polyvinylidenchloride (PVDC)/aluminium foil blisters, packed in carton packs.

Active Substance

The drug substance is silodosin its 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 IUPAC nomenclature.
Silodosin is a white to pale yellowish white powder and it is odorless. Silodosin can exist in three polymorphic forms. The forms can be differentiated by IR, PXRD and solid-state ^{13}C-NMR. A well defined polymorph was selected to manufacture the finished product. Silodosin is not considered to be hygroscopic and it is very soluble in acetic acid, freely soluble in methanol, N,N-dimethylformamide (DMF), and ethanol, sparingly soluble in 1-octanol, and very slightly soluble in water. It was verified that this active substance is soluble in various buffers at acidic pH but very slightly at alkaline pH. The above-mentioned active substance has one chiral centre and is used as a single enantiomer (R).



- **Manufacture**

Silodosin is synthesised in five reactions steps. The active substance is manufactured by two manufacturers. However, it is important to underline that the synthetic process and controls on the active substance are the same for the two sources of silodosin. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by recrystallisation and the crystallised active substance is finally milled.
Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, ^{19}F-NMR spectroscopy, two dimensional NMR spectroscopy (COSY, NOESY, HMCQ and HMBC), mass spectroscopy (ESI-MS and ESI-MS/MS) and optical rotation. The proposed molecular structure was confirmed by X-ray single crystal structural analysis.

- **Specification**

The active substance specifications include tests for appearance (white to pale yellowish white powder), identification (IR, fluoride, mp), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), impurities (HPLC), assay (HPLC), loss on drying (Ph.Eur.) and residual solvents (Ph.Eur.).

All specifications reflect the relevant quality attributes of the active substance. The analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines.
Impurities were described, classified as process-related impurities and possible degradation products, and qualified. All potential genotoxic impurities were discussed and are below the qualification threshold. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances for both manufacturers were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

Three pilot-plant batches from each manufacturer of the active substance were put on long-term condition (25±2°C/60±5%RH), and accelerated condition (40±2°C/75±5%RH). At present, the stability studies for three production scale batches from each manufacturer of silodosin are currently being performed in accordance with the protocol.
All stability studies were completed according to ICH guidelines and demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: appearance, identification (IR), impurities (HPLC), optical isomer (S-isomer), water content, polymorphic form, microbial limits.
The same analytical methods have been used in the stability programme as for release. In addition, the stability studies included a specific control of polymorphic form using an X-ray powder diffraction and the determination of microbial content.
Based on the stability results it was concluded that the proposed re-test period is justified when the active substance is stored in the original packing material and protected from light.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified. The main aim of the formulation development was to obtain a composition with good homogeneity and performance (disintegration and dissolution) characteristics.

The manufacturer developed silodosin 8 mg capsules with a content which is proportionally similar in its active and inactive ingredients to the 4 mg capsules already marketed in Japan by Kissei and utilised also by Watson. It was noted that there were no changes in the manufacture of the blend of the two strengths.

Silodosin 8 mg capsules developed were used in Phase I and Phase III clinical studies.

Comparative dissolution profiles were obtained for the 4 mg and 8 mg capsules using three 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.

- **Adventitious Agents**

Neither the excipients nor the active substance is derived from human or animal origin. Certificates of Suitability were provided for the gelatine capsule which is of ruminant origin.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, granulation, sieving and capsule filling.

It was noted that the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.
The proposed commercial process was validated by a number of studies for the manufacturing process. The batch analysis data show that the medicinal product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the capsules.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, uniformity of dosage units (Ph.Eur.), identification (HPLC), assay (HPLC), impurities (HPLC), dissolution (Ph.Eur.), titanium dioxide identification (4 mg & 8 mg), iron oxide identification (4 mg) and microbial limits (Ph Eur).
All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
Batch analysis data on five (one lab and four pilot scale) batches of silodosin 4 mg and three (one lab and two pilot scale) batches of silodosin 8 mg confirms satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the ICH guideline. Two lab batches and four pilot batches for silodosin 4 mg have been stored at long term (25±2°C/60±5%RH); two lab batches and four pilot batches for silodosin 4 mg have been stored at intermediate conditions (30°C ± 2°C/65% RH ± 5% RH) and two lab batches and four pilot batches for silodosin 4 mg have been stored at accelerated (40°C±2°C, 75 ±5%RH) conditions in the proposed market packaging. Two lab batches and two pilot batches for silodosin 8 mg have been stored at long term (25±2°C/60±5%RH); two lab batches and two pilot batches for silodosin 8 mg have been stored at intermediate conditions (30°C ± 2°C/65% RH ± 5% RH) and two lab batches and two pilot batches for silodosin 8 mg have been stored at accelerated (40°C±2°C, 75 ±5%RH) conditions in the proposed market packaging.
The following parameters were controlled: appearance, assay, impurities, dissolution and microbiological contamination.
One pilot batch of each strength was stored under ICH photostability conditions and no significant changes were observed.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

Silodosin is an α1-adrenergic receptor (AR) blocker that selectively affects the prostate, urethra, and trigone of the urinary bladder in the lower urinary tract as a therapeutic agent for the treatment of the signs and symptoms of benign prostatic hyperplasia.
During development of the product, several morphological forms of the drug substance were used. The drug substance used in the pharmacology studies was the selected crystalline form of silodosin (KMD 3213). In the pharmacokinetic studies, the selected crystalline form of silodosin administered in a capsule was used in a single oral administration study in dogs. A suspension solution of the selected

crystalline form of silodosin containing a small amount of another form was used in the 7-day repeat-dose oral administration study in which the effect of silodosin on hepatic drug metabolic enzymes was studied. All toxicity studies were conducted using the selected crystalline form of silodosin, with the exception of part of the reproductive and developmental toxicity studies, which were conducted using a mixture of the selected crystalline form and another form of silodosin. There were no differences between the selected crystals and the other utilised crystals in physicochemical characteristics such as solubility, stability in water, and melting point.
Silodosin metabolites were evaluated in several studies in order to characterise their pharmacology and toxicity.

GLP aspects
Pivotal core safety pharmacology, pharmacokinetics/toxicokinetics and toxicology studies were conducted in compliance with Good Laboratory Practice.

Pharmacology

- Primary pharmacodynamics

An extensive programme of pharmacology studies has been performed; of which only the pivotal studies have been included in this assessment report.

In vitro studies
Affinity for human α1-AR subtypes was assessed in a receptor binding study using membrane fractions of mouse-derived LM(tk-) cells in which each of three human α1-adrenergic receptor (AR) subtypes (α1A-, α1B- and α1D-ARs) were expressed. Silodosin showed a high affinity for α1A-AR subtype (pKi value: 10.4). The selectivity of silodosin for α1A-AR subtype was 162 times and 55 times higher than for subtypes α1B-AR and α1D-AR, respectively. The selectivity of silodosin for subtype α1A-AR was higher compared to other α1-AR blockers tested, including tamsulosin hydrochloride, prazosin hydrochloride, and terazosin hydrochloride. The affinity for the α1A-AR subtype was highest with tamsulosin hydrochloride, followed by silodosin, prazosin hydrochloride and terazosin hydrochloride.

Another study examined silodosin actions on noradrenaline-induced contractions in various isolated tissues. Silodosin showed antagonism to noradrenaline-induced contraction in lower urinary tract tissues of rabbits including the prostate, urethra and trigone of the bladder (α1A-AR) with pA2 or pKb of 9.60, 8.71 and 9.35, respectively. The pA2 of the antagonism to noradrenaline-induced contraction for silodosin in the isolated rat spleen (α1B-AR) and isolated rat thoracic aorta (α1D-AR) were 7.15 and 7.88, respectively. The selectivity of silodosin for the prostate was approximately 280-fold higher than that for spleen and approximately 50-fold higher than that for the thoracic aorta, indicating high selectivity of the compound for the lower urinary tract tissues.

In vivo studies
The effects of silodosin on the increase in urethral pressure and mean blood pressure in rats induced by phenylephrine (a α1-AR agonist agent), were investigated *in vivo.* The characteristics of the effects were compared with those of other α1-AR blockers. Intravenous silodosin (0.3-300 μg/kg) suppressed the phenylephrine-induced increase in urethral pressure by approximately 50% at doses of 1 μg/kg and higher and decreased blood pressure by approximately 15% at doses of 10 μg/kg and higher in anaesthetised rats. Tamsulosin hydrochloride, prazosin hydrochloride and terazosin hydrochloride, also inhibited phenylephrine-induced increases in urethral pressure and decreased blood pressure, although the required doses of the three compounds were lower than that of silodosin. The three compounds also showed a greater effect on blood pressure compared to silodosin. Similarly, after intraduodenal administration silodosin (0.003-3 mg/kg) dose-dependently inhibited phenylephrine-induced increases in urethral pressure and showed hypotensive effects at higher doses in anaesthetised rats.

In another study, effects of silodosin and tamsulosin at doses of 0.1, 0.01 and 0.001 mg/kg IV on rat benign prostatic hyperplasia model were assessed. Both, silodosin and tamsulosin hydrochloride, at doses of 0.01 mg/kg and higher, inhibited overactive bladder-like symptoms.

The active substance has a chiral centre. The CHMP has expressed a concern regarding the possibility of *in vivo* chiral conversion of silodosin and its metabolites. In their responses the applicant has referred to data from the phase I clinical study (98364) which showed that the chiral centre was not a target for metabolic reactions and no inversion was detected in any sample indicating that *in vivo* isomerisation of silodosin did not occur in humans.

Metabolites
The glucuronide conjugate of silodosin (KMD 3213G) and a metabolite KMD 3293 were detected as the major metabolites in human plasma. KMD 3213G was not detected in animal plasma. KMD 3213G had 1/8 times the affinity of silodosin for human α1A-AR. In animals, this human metabolite had 1/4.5 and 1/35 times the affinity of silodosin for α1A-AR subtype in rat mandibular gland and for α1B-AR subtype in rat liver, respectively, and approximately 1/2 the inhibitory effect on contraction induced by noradrenaline in the isolated prostate in rats, and not more than 1/10 of silodosin transferability to the prostate. KMD 3293 was detected in animal plasma and had 1/42 times the affinity of silodosin for subtype α1A-AR in humans.

Secondary pharmacodynamics

A receptor binding study was conducted using animal tissues and cells expressing human receptors, i.e. rat cerebral cortex and rat striatum and human β2-AR, dopamine (D1, D2 long and D4.2) receptors expressed in Sf9 cells and rat dopamine D3 receptor expressed in Sf9 cells. Silodosin's affinity for β2-AR (pKi: 8.25) was almost equal to that for α1D-AR subtype (pKi: 8.66) and α1B-AR subtype (pKi: 8.19), but it showed affinity only at high concentrations for α2- and β1-AR, muscarinic receptor, serotonin (5-HT1) receptor and dopamine (D1, D2 long, D3 and D4.2) receptors. In general, the affinities of silodosin for other receptor subtypes were lower than that for α1A-AR.

The affinity of silodosin for β2-AR was determined in the functional pharmacological study using a uterus specimen isolated from pregnant rats. Silodosin's affinity for β2-AR was approximately 140-fold lower than for α1A-AR subtype, and the concentration required to obtain action on the pregnant uterus was higher than that required to obtain action on the prostate. In this study silodosin showed no agonist action on β2-AR and demonstrated an antagonistic action at 3×10^{-6} mol/L and above.

Metabolites
The affinity for receptors other than α1-AR was assessed in order to determine pharmacological characteristics of the glucuronide conjugate of silodosin (KMD 3213G) and KMD 3293, the two main metabolites in humans. The pKi values of KMD 3213G and KMD 3293 were less than 7 for all of the receptors other than α1-AR (see table).

Receptor	Radioactive ligand	Glucuronide conjugate K of KMD-3213K	KMD-3293
		pKi [a]	pKi [a]
α_2-AR [a]	^{3}H-RX821002	N.D.	N.D.
β_1-AR [a]	^{3}H-DHA	4.20	5.46
Muscarinic receptor [b]	^{3}H-QNB	N.D.	N.D.
Serotonin (5-HT$_1$) receptor [c]	^{3}H-Serotonin	N.D.	N.D.
β_2-AR [d]	^{3}H-CGP12177	4.96	5.04
Dopamine D$_1$ receptor [c]	^{3}H-SCH23390	N.D.	N.D.
Dopamine D$_{2\ long}$ receptor [c]	^{3}H-Spiperone	N.D.	5.19
Dopamine D$_3$ receptor [d]	^{3}H-Spiperone	6.27	5.92
Dopamine D$_{4.2}$ receptor [c]	^{3}H-Spiperone	N.D.	N.D.

Each value in the table represents pKi value in 2 animals.
N.D.: Not determined (the inhibition rate at the concentration of 1×10^{-4} mol/L was less than 50%).
[a] Each pKi value is negative logarithmic value of the mean Ki value of 2 animals (- log Ki).
[b] Rat cerebral cortex.
[c] Rat striatum.
[d] Human receptor.
[e] Rat receptor.
Concentrations of glucuronide conjugate K of silodosin used in the study: 1×10^{-7} to 1×10^{-4} mol/L (common ratio, 10; α_2-AR, β_1-AR, muscarinic receptor, serotonin (5-HT$_1$) receptor and dopamine (D$_1$, D$_{2\ long}$, D$_3$ and D$_{4.2}$) receptors) 1×10^{-10} to 1×10^{-4} mol/L (common ratio, 10; β_2-AR)

- Safety pharmacology programme

Central Nervous System
The effects of silodosin on the central nervous system were assessed in male Wistar rats (10/group) by the functional observational battery (FOB) test. Orally administered silodosin showed no effects on the central nervous system at doses up to 2 mg/kg. At 20 mg/kg, marked decreases in arousal, as well as tremors, in 2 of 10 animals were noted at the highest dose. Decreases in body temperature of approximately 1°C were observed at 0.5 to 4 h after this dose.

Respiratory System
In conscious male beagle dogs (n=5), blood haemoglobin oxygen saturation, oxygen and carbon dioxide partial pressures and pH were measured as indicators of the depth of respiration. Silodosin had no effect on these parameters after a single oral dose at 0.2, 2 and 20 mg/kg (washout period between doses – 1 week). Transient increases in respiratory rate were noted at 4 h after administration at 2 mg/kg and at 3 and 6 h after administration at the high dose. However, there was no effect on the depth of respiration at these doses. The increase in respiratory rate was not considered to be a direct action of silodosin on respiratory function.

Cardiovascular System
The hERG (human Ether-à-go-go Related Gene) tail current using HEK293 cells was determined at concentrations of 1×10^{-7}, 3×10^{-7}, 1×10^{-6}, 3×10^{-6} and 1×10^{-5} mol/L. The hERG tail current was inhibited in a concentration-dependent manner at 1×10^{-6} mol/L and higher, with an IC50 value of 8.91×10^{-6} mol/L.

In male Hartley guinea pigs myocardial action potential waveform in the papillary muscle was investigated at concentrations of 1×10^{-7}, 1×10^{-6} and 1×10^{-5} mol/L. The duration of 90% repolarisation of action potential (APD90) was prolonged by 6.4% and 17.1% at concentrations of 1×10^{-6} and 1×10^{-5} mol/L, respectively.

Conscious male beagle dogs (n=7) were used to evaluate blood pressure, heart rate and ECG after a single oral administration of silodosin at 0.2, 2 and 20 mg/kg (washout period of 7 days between doses). Silodosin did not show any effect on heart rate and ECG at 20 mg/kg. A decrease in blood pressure was observed, which was attributable to α1-AR antagonistic effect. Transient decreases in mean blood pressure and diastolic blood pressure (by 12% and 16%, respectively) were observed at 1 h post-dose at 0.2 mg/kg. At 2 mg/kg, transient decreases in mean blood pressure and diastolic blood pressure (by 13% and 12%, respectively) were observed at 1 h, and a decrease in systolic blood pressure (by up to 18%) was observed at 1 to 6 h. After administration of 20 mg/kg a decrease in systolic blood pressure (by up to 24%) at 0.5 to 8 h, a decrease in diastolic blood pressure (by up to 22%) at 1, 3, 4, 6 and 8 h, and a decrease in mean blood pressure (by up to 23%) at 0.5 to 8 h were also observed. These effects were resolved by 24 h after administration

Metabolites
Safety pharmacology studies were conducted on KMD 3213G, the main metabolite in humans that was not detected in animal plasma. KMD-3213G did not show any effect on the central nervous (rats), respiratory (dogs) and cardiovascular (dogs) systems after intravenous injections up to the dose of 3 mg/kg. In addition, no effect on hERG tail current and myocardial action potential waveform in the papillary muscle isolated from guinea pigs at concentrations up to 1×10^{-5} mol/L was observed. See below for further discussion.

- Pharmacodynamic drug interactions

No specific non-clinical pharmacodynamic drug interaction studies were conducted. Drug interactions were examined in clinical studies hence the absence of non-clinical data can be accepted.

Pharmacokinetics
The absorption, distribution, metabolism and excretion of silodosin (KMD 3213) were studied using non-labelled silodosin and radiolabelled silodosin (^{14C}KMD 3213) in ICR mice, Sprague Dawley rats

and Beagle dogs. Oral dosing was used as the main route of administration for these studies, as this is the intended clinical route. Studies using intravenous administration were also performed to investigate bioavailability (BA).
The data presented below refer to rat and dog pharmacokinetic studies as those species were used also in toxicology studies.
In the rat (oral) dose studies, radiolabelled silodosin, was dissolved in dilute hydrochloric acid, followed by dilution with a 0.5% aqueous solution of methylcellulose. For the intravenous studies, radiolabelled silodosin was dissolved in dilute hydrochloric acid followed by dilution with physiological saline. In the rat enzyme induction study, non-labelled silodosin was suspended in a 0.5% aqueous solution of methylcellulose.
In the dog (oral) dose studies, radiolabelled silodosin, was dissolved in dilute hydrochloric acid and filled into capsules. For the oral dose of non-labelled silodosin in dogs, silodosin was filled into capsules, while the salt of silodosin (KMD 3213•2HBr), dissolved in saline was used in intravenous injection studies. For the clinical pharmacological study (mass balance), radiolabelled silodosin was dissolved in dilute hydrochloric acid and administered orally.

Absorption
Single dose
In rats and dogs after single oral doses (0.3, 1 and 3 mg/kg in rats; 0.5 mg/kg in dogs) under fasting conditions silodosin was rapidly absorbed with Tmax of 0.10-0.15 and 0.88 hour, respectively. In rodents, the Cmax and AUC of silodosin increased dose-dependently but were not dose-proportional at higher levels, i.e. following 0.3 mg/kg the Cmax was 9.3 ng/ml and AUC0-∞ was 6.9 ng*hr/ml, following 1.0 mg/kg the Cmax was 28.7 ng/ml and AUC0-∞ was 27.9 ng*hr/ml, following 3.0 mg/kg the Cmax was 202 ng/ml and AUC0-∞ was 170 ng*hr/ml. In the dog following the single dose of 0.5 mg/kg the Cmax was 37.6 ng/ml and AUC0-∞ was 97.3 ng*hr/ml. The oral bioavailability was approximately 9% in rats and 25% in dogs. Plasma concentrations of silodosin were also measured after a single oral dose of 100 and 200 mg/kg under non-fasting conditions in the dog. Results showed that the exposure (AUC0-24 and Cmax) after higher doses of silodosin did not increase dose-proportionally.
In rats after single intravenous doses of 0.03, 0.1, 0.3 and 1 mg/kg under non-fasting conditions, the CLtot and Vd were 55.1 to 71.7 ml/min/kg and 4.7 to 11.4 L/kg, respectively. In dogs the CLtot and Vd after an intravenous injection of silodosin under fasting conditions were 22.3 mL/min/kg and 3.1 L/kg, respectively. The CLtot was nearly identical to the hepatic blood flow indicating hepatic blood flow-limiting pharmacokinetic.
The measurements of the plasma radioactivity of 14C-silodosin performed after a single oral dose (1 mg/kg, under fasting and non fasting conditions) and a single intravenous injection (1 mg/kg, under fasting conditions) in male Sprague Dawley rats suggested that food intake decreased the absorption of silodosin.
When exposure (Cmax and AUC) was compared between rats, dogs, and humans after a single oral dose, Cmax at 1 mg/kg in rats and 0.5 mg/kg in dogs corresponded to 4 mg in humans (half the recommended clinical dose of 8 mg per day). The AUC at 3 mg/kg in rats was approximately 1.3- to 1.5-fold higher than in humans after a single oral dose of 4 mg, while the AUC at a 0.5 mg/kg in dogs was approximately 1.2- to 2.1-fold lower compared to humans after a single oral dose of 4 mg

Repeat dose
In repeat-dose (14-day) oral studies in rats, AUC and Cmax generally increased in a dose-dependent manner reaching 163-203 ng*h/ml and 13 ng/ml after 15 mg/kg/day, 942-1194 ng*h/ml and 81-106 ng/ml after 50 mg/kg/day, and 2947-3078 ng*h/ml and 228-352ng/ml after 150 mg/kg/day. In 14-day study in dogs the AUC and Cmax values after administration of 80 mg/kg/day of silodosin were higher in males compared to females - 36977 ng*h/ml vs. 22065 ng*h/ml and 5303 ng/ml vs. 3477 ng/ml, respectively. Similarly, in longer pharmacokinetic studies (1-month studies in rats and dogs, 26-week study in rats, 13- and 52-week study in dogs) the PK indices tended to increase dose-proportionally.

Silodosin was absorbed from the entire small intestine. Reabsorption by the enterohepatic circulation was also observed.

Metabolites
In single dose studies in rats dose-proportional AUC and Cmax increases in metabolites KMD 3241 and 3289 were noted, while AUC0-24 for KMD 3295 increased more than dose-proportionally. The AUC0-24 was slightly lower in females. KMD 3295 was not detected in females and was detected at a low level in males. KMD 3293 was detected both in males and females but at low levels. In dogs after single oral dose exposure to KMD 3241 did not increase dose-proportionally, while dose-proportional increases in exposure to KMD 3289 and 3293 were noted. In repeat dose studies in rats KMD 3241, KMD 3289, KMD 3293, and KMD 3295 were detected in the plasma and showed the same biphasic elimination as silodosin. AUC0-t and Cmax values of metabolites increased in a dose-dependent manner. In dogs plasma concentrations and pharmacokinetic parameters in males were higher than those of the females. The order of metabolites starting with the highest concentration was: silodosin > KMD 3241 > KMD 3289 > KMD 3293 > KMD 3295.

Distribution
In rats after a single intravenous injection (0.03, 0.1, 0.3 and 1 mg/kg), t1/2 was 2.4 to 3.2 h. After a single oral dose (0.3, 1 and 3 mg/kg) t1/2 was 1.5 to 2.0 h. The t1/2 after a single oral dose and a single intravenous injection were 2.0 and 3.3 h, respectively in the dog, indicating rapid elimination from plasma.

In rats, following the single dose of 1 mg/kg, the radioactivity was widely distributed to the organs and tissues, and it was detected most prevalently in the liver, kidney, spleen, the gastrointestinal tract and bladder. Low radioactivity was detected in the central nervous system except for the pituitary gland. Radioactivity in plasma peaked at 4 h post-dose. By 168 h post-dose plasma levels of radioactivity were below the limit of detection suggesting no retention of radioactivity over a long period occurred in blood cells. A repeat-dose 21-day study with radiolabelled silodosin at 1 mg/kg/day has provided similar results.

The binding ratio of silodosin to human plasma proteins was 94.6% to 95.8%, which was higher than that in rats and dogs (80%). The binding ratios of KMD 3213G and KMD 3293, the major metabolites of silodosin in humans, were 91.2-92.0% and 90.2-91.9%, respectively. Silodosin, KMD 3213G and KMD 3293 bind predominantly to α1 acid glycoprotein in human plasma. Silodosin was associated with blood cells at 30% to 60% of the administered dose in rat and dog plasma and not greater than 5% in human plasma.

Metabolism

In vitro studies
In vitro studies using rat, dog, monkey, and human hepatocytes showed that KMD 3293 and KMD 3213G were predominantly synthesised in human hepatocytes accounting for approximately 43% and 36% of the administered radioactivity. KMD 3293 was produced in all animal species tested as well as humans, whereas KMD 3213G was generated in humans and monkeys.

In vivo studies
Radiolabelled silodosin (1 mg/kg) was administered in male Sprague Dawley rats and levels of metabolite radioactivity were measured in plasma and various organs and tissues. Metabolites in urine, faeces and bile collected 24 h after were also measured. The main metabolites were KMD 3310, KMD 3250, KMD 3295 and KMD 3241. KMD 3310 was the most predominant metabolite in plasma (74.7%) urine (38%), kidney (69%) and prostate (54%) and the second predominant metabolite in the liver (22%) after 30 minutes post-administration. KMD 3250 was the most predominant metabolite in the liver (25%), bile (26%) and faeces (32%). KMD 3295 was detected in bile (16%), while KMD 3241 in prostate (19%) and kidney (11%).
KMD 3213G, the main metabolite in humans, was detected in the rat liver (≤ 7% of the hepatic radioactivity). KMD 3293 was also found in the rat liver (≤ 3% of liver and bile radioactivity).

In dogs after a single oral dose of radiolabelled silodosin (0.5 mg/kg) metabolites in plasma, urine and faeces were measured. The main metabolite detected in plasma collected between 15 min and 4 h after administration was KMD 3310 (73.1 to 95.3%). KMD 3213G (the main metabolite in humans) was

not detected in plasma at any time point. KMD 3293 and KMD 3295 were detected in plasma at 1 and 1.5 h after administration (0.5% and 0.3%). KMD 3241 was present in the plasma at most sampling times and did not account for more than 4% of the radioactivity. In urine (24 h post dose), the major metabolite was KMD 3310 (82%). Metabolites KMD 3293 and KMD 3295 accounted for less than 1% of the dose, and KMD 3241 was not detected. In faeces (24 h post dose), KMD 3293 and KMD 3295 accounted for approximately 29% and 24% of the radioactivity, respectively. In faeces collected between 24 and 48 h after administration, KMD 3293 and KMD 3295 accounted for approximately 35% and 24%, respectively, of the radioactivity.

KMD 3213G was detected in dog faeces collected at 24 h and between 24 and 48 h post dose (proportion was less than 6% in both samples). KMD 3293 was detected in dog plasma and urine at a ratio of 0.5% or less, and was the main metabolite in faeces.

Studies revealed that there is a difference in metabolism of silodosin between the animals and humans; that particularly applies to the glucuronide conjugate of silodosin (KMD 3213G) not detectable in either rat or dog plasma. The applicant was asked to clarify why rat and dog were chosen as relevant species for repeat-dose toxicity studies. In their response the applicant emphasised that *in vivo* studies indicated formation of KMD 3213G (the main human metabolite) also in the studied species. Moreover, the pharmacological profile of silodosin had been already appropriately evaluated in rats and dogs: as a consequence these species were selected for toxicity studies. The applicant's response has been acknowledged by the CHMP.

Enzyme induction and inhibition
Drug metabolising enzyme activities were measured using liver microsomes from male Sprague Dawley rats (fasting) following once-daily repeat oral dose of 1, 10 and 30 mg/kg/day silodosin for 7 days. Silodosin was found to increase cytochrome P-450 levels at 10 and 30 mg/kg/day and decrease activity of aniline 4-hydroxylase and UDP-GT (at 10 and 1 mg/kg/day, respectively). No significant differences were observed in levels of microsome protein, cytochrome b5, aminopyrine N-demethylase activity, 7-ethoxycoumarin-O-deethylase activity, and glutathione S-transferase activity compared to the control. The silodosin potential to inhibit and/or induce CYP P450 as well as interactions with the drugs that are likely to be used in combination and may affect the metabolism via CYP3A4 were studied with the use of human biomaterials (see clinical part of the report for more detail).

Excretion
After a single oral dose of 1 mg/kg of radiolabelled silodosin in male rats under fasting and non-fasting conditions, the remaining radioactivity levels in excreted urine and faeces, expired air and carcass up to 168 h after administration were measured. More than 95% of the administered radioactivity was excreted in urine, faeces and expiration in 168 h after administration under fasting conditions. Corresponding fractions of administered radioactivity were 15.3%, 81.7% and 0.5%, respectively indicating that the main route of elimination in rats was in the faeces. A single-dose study and repeat-dose 21-day study under non-fasting conditions in rats, and a single-dose (0.5 mg/kg) study under fasting conditions in dogs yielded similar results.

Additionally, results from mass balance study in healthy volunteers under fasting conditions indicated that the fraction of radioactivity excreted in faeces after a single oral dose was also higher compared to urine.

Results from studies with radiolabelled silodosin suggest enterohepatic circulation of the drug.

Pharmacokinetic drug interactions
The applicant provided no non-clinical data of pharmacokinetic drug interactions. However clinical drug interactions studies have been conducted. As there is adequate clinical data regarding drug interactions, the absence of non-clinical data can be accepted.

Toxicology

Main toxicology studies performed by the applicant are summarised in the table below.

Type of Study	Test System/N	Method of Administration	Doses (mg/kg)	Study No.
Single dose study	Rats 5/sex/group	Forced oral	500, 1000, 2000	00229
Single dose study	Rats 5/sex/group	Forced oral	400, 800, 1600	10017
Single dose study	Rats 5/sex/group	Intravenous	60, 75, 90	10092
Single dose study	Dogs 2M/group	Forced oral	1500, 2000	00233
Single dose study	Dogs 2M/group	Forced oral	1000, 1500	10025
Single dose study	Dogs 2M/group	Intravenous	25, 50	10093
1 month dose study	Rats 15/sex/group	Forced oral	0, 20, 60, 200, 600	10026
3 month rat study	Rats 10/sex/group	Forced oral	25, 100, 400	10077
26-week dose study (1)	Rats 20/sex/group	Forced oral	0, 15, 60, 300	10081
26-week dose study (2)	Rats 20/sex/group	Forced oral	1, 5	10111
2-week dose study	Rats 10/sex/group	Intravenous	2, 10, 50	10242
1 month dose study	Dogs 4/sex/group	Forced oral	25, 100, 400	10008
13-week dose study	Dogs 3/sex/group	Forced oral	10, 50, 100/200	KSI 70/970908
52-week dose study	Dogs 4/sex/group	Forced oral	5, 20, 80	KSI 71/974423
2-week dose study	Dogs 3/sex/group	Intravenous	1, 5, 25	10236

- Single dose toxicity

Single dose toxicity of silodosin was assessed after oral administration of 400, 800, and 1600 mg/kg, and intravenous administration of 60, 75 and 90 mg/kg to male and female Sprague-Dawley rats (5/sex/group). Noteworthy findings after oral administration included: lachrymation, ptosis, salivation, deep respiration, crouching posture, decreased locomotor activity, mucoid faeces and stained fur, trembling and coldness to the touch, prone position and no faeces, decreased body weight in males and decreases in body weight gain in females. In decedent animals, clonic convulsion, dyspnoea and gasping, shallow respiration and bradypnea were observed. White lesions in the liver, vacuolar degeneration in the portal area and focal necrosis of the liver were also noted in decedent animals. No abnormal changes were observed in animals that survived through the observation period. Similar overt signs of toxicity were noted after IV administration, there were however no necropsy findings.

In male beagle dogs (2/group) after single oral doses of 1000 and 1500 mg/kg overt signs of toxicity consisted of redness of auricular, ptosis, conjunctival congestion, relaxation of nictitating membrane, faecal abnormality and vomiting, decreased rectal temperature and decreased heart rate, relaxation of the anus and muscle weakness, decrease in body weight. Decreased red erythrocyte, haemoglobin and haematocrit, decreased albumin and sodium and increased total cholesterol and triglyceride were noted in the surviving animal at 1500 mg/kg. These changes returned to normal by the end of observation period. Erosion, ulcer and haemorrhage lesions were noted in the stomach and gastrointestinal mucosa in the animals that died and histopathological examinations showed erosion of the stomach and small intestinal mucosa. At single intravenous doses of 25 and 50 mg/kg, overt signs of toxicity consisted of staggering gait, decreases in locomotor activity and foamy vomit at both doses, while the inability to stand/walk was seen, trembling, lateral position, general muscle weakness, muscle weakness of hind limbs, deep respiration, conjunctival congestion, redness of auricular, relaxation of the nictitating membrane, lacrimation, salivation, vomiting-like behaviour, diarrhoea, loose stools and mucoid faeces were observed at 50 mg/kg.

The oral LD50 value was estimated to be 878 mg/kg in both male and female rats. The approximate lethal doses after a single-dose intravenous administration of silodosin were 75 mg/kg and 90 mg/kg,

respectively in males and females. In male dogs the approximate lethal dose was 1500 mg/kg orally and 50 mg/kg intravenously.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity was assessed in several studies of varying duration (2 weeks – 52 weeks) in which a wide range of oral doses have been administered (1-600 mg/kg/day) to rats and dogs.

Rats
Noteworthy findings in rats seen across all studies irrespective of the dose administered included lachrymation, ptosis and salivation in both sexes. Decreased body weight and food consumption were generally observed in male rats while at higher doses (>300-400 mg/kg) increases in food consumption and body weight were noted in females.

In 3-month and 26-week studies loose stools and diarrhoea were observed at higher doses (>300 mg/kg/day) in both sexes. In the 26-week study occasionally decreased locomotor activity and prone positions were noted in both sexes at 300 mg/kg/day. Paraphimosis and deep respiration was noted in all males at >60 mg/kg/day. Deep respiration was also observed at all doses in females.

In one-month study increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and decreases in triglycerides were noted in males at 600 mg/kg/day. Similarly, decreases in triglycerides and free fatty acids, together with increases in blood glucose, albumin and inorganic phosphorus were noted in 3-month and 26-week studies. Decreased daily excretion of sodium was noted in males at 600 mg/kg/day in the one-month study, while an increase in urinary volume was observed in males at 300 mg/kg/day in the 26-week study.

Macroscopically, changes in the liver appearance including a clear lobular pattern, yellow/pale colouring, white granular changes as well as enlargement of the liver were noted predominantly in males (≥5 mg/kg/day), while increased liver weight was seen in both sexes across all studies (≥200 mg/kg/day). In the one-month study mild enlargement of the thyroid in females at >200 mg/kg/day and males at 600 mg/kg/day, increased thyroid weight in both sexes at 600 mg/kg/day and minor haemorrhage lesions in the stomach in both sexes at 600 mg/kg/day were observed. In the 3-month study increased adrenal weights were noted in males at >100 mg/kg/day and females at 400 mg/kg/day and decreased thymus weight were noted in both sexes at 400 mg/kg/day. Increased adrenal weight was seen in males at 60 mg/kg/day also in the 26-week study, while increased ovary weight and decreased uterus weight was noted in females at 300 mg/kg/day.

Histopathological findings seen across the studies included fatty degeneration of hepatocytes in both sexes, eosinophilic degeneration of centrilobular hepatocytes predominantly in males, and enlargement of hepatocytes in both sexes (≥1 mg/kg/day). In males hyperplasia of the connective tissue and focal fibrosis were also observed (≥300 mg/kg/day). Electron microscopy showed moderate to severe increases of lipid droplets in hepatocytes in males and hyperplasia of smooth-surfaced endoplasmic reticulum in both sexes (≥100 mg/kg/day). An increase in hepatic cytochrome P-450 enzymes was also noted in males in the one-month study and in both sexes in the 26-week study. In the 3-month and 26-week study moderate microgranuloma was seen in the liver. Hypertrophy of vaginal mucosal epithelial cells, hyperplasia of the mammary gland and increased lactation activity, together with atrophy of the uterus were noted in females (≥60 mg/kg/day). Atrophy of the gastric fundic gland and oedema of the submucosal layer of the glandular stomach was seen in both sexes in the one-month study. In the 26-week study extended adrenocortical regions were seen in males.

In the one-month study during the recovery period reversal of the mild fatty degeneration of hepatocytes was not seen in males previously treated at 600 mg/kg/day. Recovery was shown for all other findings.

In general, a dose proportional increase in AUC and Cmax was seen. The NOAEL was considered to be 20 mg/kg/day in the one-month study, 25 mg/kg/day in males and 100 mg/kg/day in females in the

3-month study, less than 15 mg/kg/day in males and 60 mg/kg/day in females in 26-week study and 5 mg/kg/day in 26-week study with low doses of silodosin.

In the 2-week intravenous study in rats silodosin was given at 2, 10 and 50 mg/kg/day. Six males and 4 females at 50 mg/kg/day died during the study (immediately after dosing). In these animals, overt signs of toxicity consisted of clonic convulsions and gasping (just after drug administration). In surviving animals (both sexes) ptosis starting just after administration was noted at all doses, deep respiration at ≥10 mg/kg/day and prone position and decreased locomotor activity were observed at 50 mg/kg/day. The NOAEL was considered to be 10 mg/kg/day since death occurred at 50 mg/kg/day.
No histopathology was conducted.

Dogs
In dogs (both sexes) overt toxicity findings seen across the studies consisted of relaxation of nictitating membranes, conjunctival congestion, ptosis, trembling and liquid stools, ataxic gait or abnormal gait, vomiting and salivation, lateral position was occasionally observed (≥10 mg/kg/day). Decreased body weights were also observed. The duration and severity of these symptoms usually decreased throughout the duration of the studies. In the dog 1-month study with one month recovery, prolonged PR and QT intervals were noted on the electrocardiogram (ECG) at 400 mg/kg/day. In the same study decreases in heart rate and blood pressure were observed in both sexes. However these effects were not noted in the 13-week and 52-week study. Refer to the discussion on the non-clinical aspects section for further detail.

Changes in haematology parameters were observed in the one-month and 52-week study. They included increased fibrinogen, platelet counts and neutrophils, decreased lymphocytes, eosinophils, reticulocytes, erythrocyte counts, haemoglobin and haematocrit (≥80kg/mg/day). Bone marrow analysis showed increased immature neutrophils and an increased granulocyte/erythrocyte cell ratio, as well as a slight decrease in the percentage of polychromatic erythroblasts in males at 400 mg/kg/day.

Increased total cholesterol and α-globulin ratios were noted in both sexes at ≥100 mg/kg/day in the 1-month study while decreases in triglycerides, total cholesterol and albumins were seen in females in the 13-week study (≥50 mg/kg/day). In the one-month study at 400 mg/kg/day increased urea nitrogen and decreased total protein, sodium, potassium and chloride were noted in both sexes. Increased alkaline phosphatase in males and increased AST (GOT), ALT (GPT) and creatinine in females were also noted at this dose. Decreased creatine phosphokinase was also noted in males at 100 and 400 mg/kg/day and in females at 400 mg/kg/day. In the 52-week study decreased urea nitrogen was seen in both sexes and increased chloride was noted in females at this dose. Urinalyses showed decreased sodium in both sexes at 80 mg/kg/day. Faecal occult blood tests were positive in both sexes at 400 mg/kg/day in the one-month study.

Macroscopically, changes in the liver appearance including clear hepatic lobular pattern, darkened colour, sinusoidal dilation and congestion of the liver were seen across the studies (≥20 mg/kg/day). An increase in relative liver weights was noted (≥80 mg/kg/day). Erosions, haemorrhage and ulcers of gastric mucosa were observed in the one-month study (≥100 mg/kg/day). Atrophy of the thymus, enlargement of the adrenal cortex, fibrin adhesion and congestion of the gut, increases in adrenal and kidney weights and a decrease in thymus weights were noted across the studies (≥50 mg/kg/day). A degeneration of seminiferous tubular epithelium was noted in males at all doses in the one-month study.

Histopathologically, an enlargement of hepatocytes, atrophy of the thymus, erosions of gastric mucosa and delayed maturation of the genital organs were observed across the studies (≥50 mg/kg/day). These findings were also observed in dead animals and those sacrificed for humane reasons. In the 52-week study a dose-dependent increase in deposition of yellow or brown lipofuscin-like materials in hepatocytes in both sexes was noted at all doses. Depositions of brown lipofuscin-like materials were observed in tubular epithelial cells of the renal cortex in males at all doses and in females at ≥20 mg/kg/day. Refer to the discussion on the non-clinical aspects section for further detail.

In the one-month study findings in the recovery animals included decreased prostate weights and degeneration of seminiferous tubular epithelium in males at ≥100 mg/kg/day, increased platelet counts in females at 100 mg/kg/day and males at 400 mg/kg/day, increased fibrinogen levels, decreased thymus and testis weights, enlargement of hepatocytes, and atrophy of the thymus in males at 400 mg/kg/day. However, there were no noticeable findings in animals at 25 mg/kg/day, indicating a favourable recovery at this dose.

In general, a dose proportional increase in AUC and Cmax was seen with a plateau observed in the one-month study at ≥100 mg/kg/day. There were no major sex differences in the PK indices in other studies. The NOAEL was considered to be 25 mg/kg/day in the one-month study, 10 mg/kg/day in the 13-week study and 20 mg/kg/day in 52-week study. In the one-month study one male and two females at 400 mg/kg/day died, and one male and one female were killed in a moribund state for humane reasons. In the 13-week study one male at 200 mg/kg/day was killed (humane sacrifice).

In the 2-week intravenous study 1, 5, 25 mg/kg/day were given to male and female Beagle dogs (3/sex/group) for 2 weeks. Overt signs of toxicity were similar to those observed in oral studies and started at 25 mg/kg/day. Increased heart rates were noted on Day 7 in males at ≥5 mg/kg/day. Decreased erythrocyte counts, haemoglobin and haematocrit were noted in females at 25 mg/kg/day and decreased triglycerides were noted in males at ≥5mg/kg/day and females at 25 mg/kg/day. Increased liver weights were noted in females at all doses and increased pituitary and lung weights were noted in females at ≥5 mg/kg/day. Dose proportional increases in the AUC0-24 and Cmax were noted. There was no sex difference. The NOAEL was considered to be 25 mg/kg/day.

- Toxicokinetic data

In rats and dogs, there were occasional differences (which were sometimes marked) in exposure between males and females. There was no evidence of accumulation.

Species	Sampling Time	Dose Levels (mg/kg)	Exposure			
			Male		Female	
			C_{max} (ng/mL)	AUC_{0-t} (ng-h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng-h/mL)
Human (70kg, bw)	7 days	0.114	61.6	373.4	NA	NA
Repeat-Dose Toxicity						
Rat	Month 1 [a]	20	342.00	701.33 [b]	206.48	531.68 [b]
		60	857.75	2,567.67	757.65	1,857.70
		200	3,461.13	11,150.89	1,619.27	4,105.87
		600	9,431.37	24,241.20	2,329.84	7,518.73
	Week 26 [c]	1 [a]	2.9	NE	2.4	NE
		5 [a]	66.5	NE	21.0	NE
		15	321.65	NE	192.29	NE
		60	1,443.37	NE	1,098.13	NE
		300	3,810.00	NE	3,501.65	NE
Repeat-Dose Toxicity (continued)						
Dog	Month [d]	25	4,944.39	31,138.51 [e]	4,695.09	24,188.37 [e]
		100	15,066.04	158,780.05	13,023.07	122,309.42
		400	9,857.32	157,038.61	19,738.73	159,358.79
	Week 13 [f]	10	1,017.2	3,350 [e]	995.7	3,063 [e]
		50	4,813.1	30,096	5,918.5	25,627
		100/200 [g]	7,698.6	39,327	5,961.2	38,975
	Week 52 [h]	5	229.4	1,082 [e]	129.6	582 [e]
		20	1,489.3	7,301	1,017.6	4,628
		80	2,972.6	19,147	7,237.1	44,097

Mouse	Week 26 [i]	20/60 [j]	14.08	229 [e]	168.04	2,543 [e]
		60/150	167.94	1,897	1,476.31	16,298
		200/400	1,794.22	22,810	4,189.61	64,058
Rat	Week 26 [k]	15	34.49	422 [e]	23.85	261 [e]
		50/80 [j]	115.66	2,011	152.49	2,235
		150/250	675.78	9,509	471.91	8,282
Reproductive Toxicity						
Rat	Month 1 [l]	20	NA	NA	NE	531.68 [b]
Rabbit	Day 13 (GD 18) [m]	20	NA	NA	103.80	209.37 [o]
		60	NA	NA	562.87	1,130.88
		200	NA	NA	3,879.66	9,056.41

a) Study 10026; b) AUC0-4; c) Study 10081; d) Study 10008; e) AUC0-24; f) Study KSI 70/970908;
g) The test article was administered at the initial dose of 200 mg/kg, which was decreased to 100 mg/kg on Day 7.
h) Study KSI 71/974423; i) Study KSI 100/012988 (female study) and KSI 114/012990 (male study);
j) male/female; k) Study KSI 102/012989; l) Study 10072; m) Study 10050; n) Study 10111;
o) AUC0-6. NA = Not applicable; NE = Not evaluated.

Comparison of NOAELs and corresponding pharmacokinetic indices in repeat-dose studies and the recommended clinical dose of silodosin are presented below.

Species	**Study No.**	**Treatment Period**	**Dose** (mg/kg/day)	**NOAEL** (mg/kg/day)	**Cmax** (ng/mL)	**Safety margin in term of Cmax**	**AUC** (ng*h/mL)	**Safety margin in term of AUC**
Rat	10026	1 month	20, 60, 200, 600	male: 20 female: 20	male: 342.00 female: 206.48	male: 5.6 female: 3.4	male: 701.33 female: 531.68	male: 1.9 female: 1.4
	10077	3 months	25, 100, 400	male: 25 female: 100	Toxicokinetics: not available			
	10111	26 weeks	1, 5	male: 5 female: 5	male: 66.5 female: 21.0	male: 1.08 female: 0.34	male: NE female: NE	male: --- female: ---
Dog	10008	1 month	25, 100, 400	male: <25 female: <25	male: 4944.39 female: 4695.09	male: <80 female: <76	male: 31138.51 female: 24188.37	male: <83 female: <65
	KSI 70/970908	13 weeks	10, 50, 200/100	male: 10 female: 10	male: 1017.2 female: 995.7	male: 17 female: 16	male: 3350 female: 3063	male: 9.0 female: 8.2
	KSI 71/974423	52 weeks	5, 20, 80	male: 20 female: 20	male: 1489.3 female: 1017.6	male: 24 female: 17	male: 7301 female: 4628	male: 20 female: 12
Human (male)	SI06004	7 days	0.114*	---	61.6	---	373.4	----

NE = Not evaluated
*: Recommended clinical dose (calculated assuming that 8mg is given once daily and the human body weight is 70)

In the repeat-dose toxicology studies the Cmax safety margin ratios varied between >1 and 5.6 for female rats and 17 and <80 for female dogs. The AUC safety margins were approximately 2 for male rats and between 9 and <83 for male dogs.

- Genotoxicity

The genotoxicity of silodosin was studied in the standard battery of tests. Results are summarised in the table below.

Type of test/ Study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system		Results Positive/negative/equivocal	
Gene mutations in bacteria (10036)	*Salmonella* strains TA98, TA100, TA1535, TA1537 *E Coli* strain WP2 *uvrA*	-S9 (rat)	46.9, 93.8, 187.5, 375, 750 1500 and 3000 µg/plate.	Negative	Negative
		+S9 (rat)	46.9, 93.8, 187.5, 375, 750, 1500 and 3000 µg/plate.	Negative	Negative
Mutation assay in Mouse lymphoma cells (L5178Y) (Study KSI 80/973223)	Mouse lymphoma cells (L5178Y) Test 1	-S9	60, 125, 250 and 375 µg/mL	Negative	Negative
		+S9	60, 125, 200 and 300 µg/mL	Negative	
Mutation assay in Mouse lymphoma cells (L5178Y) (Study KSI 80/973223)	Mouse lymphoma cells (L5178Y) Test 2	-S9	150, 200, 250 and <u>300</u> µg/mL	Positive	Positive
		+S9	200, 250, 300 and 350 µg/mL	Negative	
Chromosomal aberrations in mammalian cells *in vitro* (Study 2626 (005-013))	Chinese hamster lung-fibroblast cells (CHL cells)	-S9	24-48 h incub conc's: 21.9, 43.8 and 87.5 µg/mL	Negative	Positive
			24-48 incub conc's: 50, 200, 350 and <u>500</u> µg/mL	Positive	
		+S9	24-48 incub conc's: 87.5, 175 and 350 µg/mL	Negative	
Additional Chromosomal aberrations in mammalian cells *in vitro* (Study 7L425)	Chinese hamster lung cells (CHL/IU cells)	-S9	37.5, 75, 150, 300 and <u>600</u> µg/mL.	Positive	Positive
Unscheduled DNA synthesis *in vivo* (Study KSI 083/974372)	Rat SD hepatocytes	2 and 14 hrs after single oral dosing with 600 and 2000 mg/kg		Negative	Negative
Chromosomal aberrations *in vivo* (Study 10067)	ICR mice, micronuclei in bone marrow	Single oral dose: 0; 250, 500 and 1000 mg/kg		No increase in number of micronuclei.	Negative

Metabolites

- Reverse mutation test of the glucuronide conjugate of silodosin in bacteria.

Salmonella typhimurium TA98, TA100, TA1535 and TA1537, and Escherichia coli WP2uvrA/pKM101 were used and the test was conducted using the preincubation method with and without metabolic activation. Concentrations of 156 – 5000 and 78 – 2500 µg/plate were used without and with metabolic activation, respectively. No increase over 2-fold was observed in the number of revertant colonies compared with the vehicle control with or without metabolic activation. KMD 3213G was not considered mutagenic under these test conditions.

- Chromosomal aberration test of the glucuronide conjugate of silodosin with mammalian cells in culture

Chinese hamster lung-cells (CHL/IU cells) were used in this study and concentrations of 1250, 2500 and 5000 μg/ml both for short-term treatment with and without metabolic activation and continued treatment without metabolic activation were used to observe chromosome responses. No significant increases were noted in the frequency of cells with structural chromosome aberrations or that of polyploid cells, compared the control. KMD 3213G did not induce chromosomal aberrations under these test conditions.

In conclusion, there was a slight increase in the number of chromosomal aberrations in mammalian cells in the absence of metabolic activation. Further analysis demonstrated a decrease in the mitotic index indicative of cellular toxicity. Although an increase was noted in the Mouse lymphoma mutation assay (Test 2) it was not reproducible. This increase, therefore, was not considered to be significant in terms of the evaluation of genotoxicity. Moreover, silodosin and its glucuronide conjugate were not mutagenic in other tests. Hence, the weight of evidence suggests that silodosin is not genotoxic.

- Carcinogenicity

The carcinogenicity of silodosin was studied in mice (50/sex/group) and rats (60/sex/group) in 104-week studies. The findings noted in females, although not directly relevant as silodosin is indicated in males only have been included in this report for completeness. The administered doses were 60, 150 and 400 mg/kg/day in female mice, 20, 60, and 200/100 mg/kg/day in male mice, 15, 80 and 250 mg/kg/day in female rats and 15, 50 and 150 mg/kg/day in male rats. All studies were by dietary administration and the doses stated are estimated target doses.

In female mice, neoplastic lesions included mammary adenocarcinomas, and adenoacanthoma in mice treated at 150 mg/kg/day and higher; and non-statistically significant increases in pituitary and hepatocellular adenomas in animals treated at 400 mg/kg/day. Non-neoplastic findings included uterine adenomyoma at all doses, mammary atypical hyperplasia, lobular hyperplasia, squamous cell metaplasia, increased cystic uterine glands, and decreased cystic endometrial hyperplasia at ≥150 mg/kg/day, diffuse or focal hyperplasia and focal hypertrophy of the anterior lobe of the pituitary, dilation of the mammary acinus and duct, and increased dilation of the uterine gland at 400 mg/kg/day. These findings appeared to be related to increased prolactin production. Prolactin levels were increased either at one dose or multiple doses over 14-24 days. Increased liver and pituitary weights and decreased uterus and cervix weights were observed at ≥150 mg/kg/day. AUC0-24 and Cmax at week 26 showed greater than dose proportional increases at ≥150 mg/kg/day.

In male mice no increase in neoplastic lesions or tumour development were noted. Non-neoplastic lesions included dilated seminal vesicles and coagulating glands as well as increased interstitial infiltration of lymphocytes at all doses. Decreased heart weights were noted at all doses and increased epididymis weights were noted at ≥60 mg/kg/day, along with decreased prostate weights at 100 mg/kg/day. AUC0-24 and Cmax values at week 26 increased more than dose proportionally at ≥60 mg/kg/day.

In male rats, neoplastic lesions included statistically significant increases in thyroid follicular cell adenomas as well as combined thyroid follicular cell adenomas and carcinomas in males at 150 mg/kg/day. Non-neoplastic lesions included increased hypertrophy of thyroid follicular cells in males at all doses and in females at 250 mg/kg/day. Increased cystic hyperplasia of thyroid follicular cells was also noted in males at 150 mg/kg/day. Based on the results from mechanistic studies these tumours were thought to be related to increased UDP-GT levels and disturbances of the T3 and T4 metabolism. Toxicology findings were similar to those observed in single- and repeat-dose studies. AUC and Cmax values at week 26 increased dose-proportionally with the exception of the highest dose of 250 mg/kg/day in females. Refer to the discussion on the non-clinical aspects for further detail.

- Reproduction Toxicity

In the study assessing fertility and early embryonic development doses of 20, 60, 200 and 600 mg/kg/day were administered to male Sprague Dawley rats before mating (64 days) and through the mating period until the day before necropsy and to females for 15 days before mating, through the

mating period and up to Day 7 of gestation. Decreased fertility rate was noted in males at all doses, and a decreased mating rate was observed in males at ≥200 mg/kg/day. In females, findings included a decreased fertility rate at all doses, prolonged or disappeared oestrous cycle at ≥60 mg/kg/day, decreased mating rate at ≥200 mg/kg/day and decreased implantation index at 20 and 600 mg/kg/day. Decreases in foetal body weight were also noted at 600 mg/kg/day. No treatment-related changes in the number of corpora lutea, sex ratio and foetal anomalies were noted. In order to determine whether a decrease in fertility and early embryo development were caused by males or females two studies in which treated males were paired with untreated females were performed. In the first one (Mating I) the highest dose of 600 mg/kg/day was chosen while in the second one (Mating II) the highest dose of 20 mg/kg/day was selected. A third study in which females treated with the highest dose of 20 mg/kg/day were paired with untreated males was also conducted. Noteworthy findings in the first two studies included decreased sperm counts and decreased viable sperm numbers at 600 mg/kg/day, decrease in the fertility rate at 20, 60 and 600 mg/kg/day, aspermatogenesis at ≥200 mg/kg/day, decreased implantation index at all doses. In males treated with lower doses (Mating II) recoverability was confirmed. In the third study (study in female rats) there were no test article-related effects on caesarean section examinations. The NOAEL for general toxicity and reproductive functions of male animals and early embryo development was considered to be 6 mg/kg/day. The NOAEL for general toxicity of female animals was considered to be 6 mg/kg/day, while the NOAEL for reproductive function of females and early embryo development was considered to be 20 mg/kg/day. This information is adequately reflected in the SmPC.

Silodosin was not teratogenic in rats given up to 1000 mg/kg/day from Day 7 to Day 17 of gestation. The NOAEL for general toxicity of dams was estimated to be less than 30 mg/kg/day, while the NOAEL for reproductive function in dams and embryo-foetal development was estimated to be 1000 mg/kg/day. Teratogenicity was not observed in rabbits at doses up to 200 mg/kg/day (Day 6 to Day 18 of gestation). 4 cases of abortion in the late stages of gestation along with emaciation, decreased body weight and food consumption were observed at 200 mg/kg/day. These finding were not seen at any other dose. Decreased foetal weight and placental weight, and increased post-implantation loss were attributed to decreased food consumption in dams at 200 mg/kg/day. The NOAEL for dams and embryo-fetal development was considered to be 60 mg/kg/day.

In the study assessing prenatal and postnatal development, including maternal function daily oral doses of silodosin were given to female SD rats from Day 7 of gestation to Day 20 after delivery. A high dose of 300 mg/kg/day was selected for this study (other doses selected were 10, 30 and 100 mg/kg/day). No test article-related effects were observed on maternal body weight. No test article-related effects were noted in nursing by dams, post-natal growth, development and reproductive functions of offspring, and development in the next generation (F2). The NOAEL was considered to be 10 mg/kg/day for general toxicity of dams (F0), 30 mg/kg/day for maternal function in dams, and 300 mg/kg/day for the offspring (F1).

- Local tolerance

Intravenous, perivenous and intra-arterial tolerance studies using silodosin for injection (0.2 mg/ml) were carried out to support a clinical pharmacology study (BA / influence of food intake). Silodosin for injection showed a very minor haemolytic effect (0.4 – 0.6%) and muscle damage. Nevertheless, no specific concerns derive from the local tolerance studies.

- Other toxicity studies

The applicant has conducted several additional toxicity studies including phototoxicity studies, antigenicity studies, immunotoxicity studies, studies on impurities and numerous mechanistic studies.
In vitro and *in vivo* phototoxicity studies suggest that silodosin may have the ability to minimally increase sensitivity to sunlight. From the data presented the effects seen were mild in nature and seemed to be a high dose phenomenon. This information is adequately reflected in the RMP.

Silodosin was considered not to have antigenic potential in guinea pigs.

The evaluation of potential adverse effects of silodosin on the immune system was incorporated in the repeat-dose toxicity tests. Effect of repeat-dose treatment with silodosin on the immune system such as the morphology of thymus and lymph nodes were assessed. The observed changes were generally not dose limiting (apart from mortality and body weight) and can be attributed to the study-related stress.

Metabolites
Toxicity of glucuronide conjugate of silodosin was assessed in a single-dose (10 and 50 mg/kg) and 2-week (2, 10 and 50 mg/kg/day) intravenous dose study in rats. The lethal dose of KMD 3213G in the single-dose study was considered to be 50 mg for both sexes with no practical difference in the lethal dose compared to silodosin.

In the 2-week intravenous study in rats the toxicology findings were similar to those observed in the repeat-dose toxicity studies. Toxicokinetic examinations showed a higher exposure to KMD 3213G compared with silodosin. The Cmax and AUC of KMD 3213G given at 50 mg/kg/day were 530-and 10-fold higher than the respective indices in humans given at the recommended clinical dose. Under this condition, the toxicity of KMD 3213G was considered to be qualitatively and quantitatively similar to, or less severe than that of silodosin. It should however be noticed that the CHMP has expressed concern whether 2-week study has been of sufficient duration to evaluate the toxicity of the glucuronide metabolite. Responses provided by the applicant underlined that the toxicity observed with KMD 3213G was similar to that of silodosin in the circumstances where sufficient systemic exposure exceeding that achieved in human has been reached after the iv administration of the drug.

Furthermore, a 4-week oral dose study in dogs (25 mg/kg/day) was performed in order to assess the accumulation of metabolites KMD 3241 and 3289 in the liver and kidney. As the concentrations of metabolites were considered to reach the steady state on Day 21 it was concluded that no accumulation in the liver and kidney was observed.

Metabolites KMD 3241 and KMD 3289, were identified as a degradation products and were commonly seen in stability test results. Exposure to KMD 3241 as a metabolite was confirmed after single and repeat oral toxicity studies in the rodents and dogs, therefore this metabolite has been adequately evaluated. In addition genotoxicity micronucleus test with mice and an UDS test with rat hepatocytes have been conducted with KMD 3241 and KMD 3289. Sufficient toxicity data has been provided to support qualification of these degradation products/metabolites.

Ecotoxicity/environmental risk assessment

The applicant has submitted the Fpen value of 0.181 % based on recently published pharmacoepidemiological data taking into account the whole male population from >45 years in the entire EU 25 (Eurostat). The revised estimate of Fpen based on published pharmacoepidemiological data has been rounded up to 0.2%, which is associated with a PECsurfacewater of 0.008 µg/L. It was concluded that the updated ERA provides clarification that the PECsurface water for silodosin was less than the action limit of 0.01 µg/L, and therefore a phase II assessment was not required. Consequently, it was considered that the use of silodosin for the treatment of BPH is unlikely to pose a risk to the environment.

Discussion on the non-clinical aspects

The non-clinical pharmacology, pharmacokinetics and toxicology of silodosin have been studied extensively. The product shows high affinity for alpha-1 adrenergic receptors (subtype A) in the lower urinary tract causing relaxation of the prostate capsule, urethra and trigone of the urinary bladder. This action supports the indication of silodosin in the treatment of signs and symptoms of benign prostatic hyperplasia. The affinity of silodosin for other alpha-receptors (subtypes B and D) has been demonstrated to be 50-160-fold lower indirectly indicating a lower risk of alpha-receptor- mediated adverse events, e.g. orthostatic hypotension. Silodosin showed no effect on the central nervous system of rats at doses up to 2 mg/kg. At 20 mg/kg trembling, decreased awakening levels and body temperature were observed.

In vitro silodosin inhibited hERG tail current and prolonged the APD90 in the papillary muscle isolated from guinea pigs. Furthermore, it decreased blood pressure at 0.2 mg/kg in the safety pharmacology study and prolonged PR and QT intervals at 400 mg/kg/day in the 1-month toxicology study in dogs. Therefore, the CHMP requested the applicant to discuss these findings. The responses underlined that no effects on the heart rate and ECG and blood pressure were observed at doses up to 20 mg/kg in the 52-week study corresponding to AUC safety margin of 20-fold and 12-fold in males and females, respectively. Similarly, no abnormality in the ECG was noted in the 13-week study. The CHMP has therefore acknowledged that silodosin is unlikely to cause a significant decrease in blood pressure and has little effect on the repolarisation process of the heart.

Pharmacokinetic studies revealed a difference in metabolism of silodosin between animals and humans. This particularly applied to the glucuronide conjugate of silodosin, the main metabolite in human plasma. It has been concluded that due to the fact that the pharmacological profile of silodosin and its metabolites had been already thoroughly evaluated in rats and dogs those species would be appropriate for the toxicology studies.

In the single-dose toxicity studies the oral LD50 value was estimated to be 878 mg/kg in both male and female rats. The approximate lethal doses for male and female rats receiving a single iv dose were 75 mg/kg and 90 mg/kg, respectively. The findings observed in the repeat-dose toxicology studies were related to enzymatic induction in the dog liver (fatty degeneration), increased prolactin production (changes in mammary gland and sex organs in female rats), stress (atrophy of the thymus and lipid accumulation) or were considered a high dose phenomenon (atrophy of the fundic gland and oedema of stomach submucosa in rats and dogs). In dogs degeneration of the seminiferous tubular epithelium and delayed maturation of male genital organs were observed. These findings were not considered to be significant in terms of human safety since no changes in male reproductive organs were observed in the 52-week oral dose study and there was a sufficiently wide safety margin between the NOAEL in dogs and the recommended human clinical dose.

In the 52-week oral dose study in dogs the deposition of lipofuscin-like materials, in hepatocytes in both sexes was noted at all doses with no histopathological correlates or blood biochemical changes. No clear signal of liver toxicity was observed in clinical trials; however impaired hepatic function and jaundice have been reported from post-marketing use of silodosin in Japan. Therefore the CHMP requested that the applicant provide a more robust scientific discussion of these findings and their relevance to man. Following the applicant's response the CHMP agreed that the findings were not considered of toxicological significance and relevant to man as 1) the severity was minimal or slight, 2) this finding was observed in dogs only, and 3) no other histopathological findings and blood biochemical changes suggestive of hepatotoxicity were observed.

Silodosin was considered not to be genotoxic in a standard battery of tests.

Neoplastic lesions observed in female mice, including mammary adenocarcinomas, adenoacanthoma, pituitary adenomas appeared to be related to the increased prolactin production as discussed by the applicant in responses to the CHMP questions. In male rats, an increase in incidence of thyroid follicular cell tumours was noted. The discussion provided by the applicant indicated that these tumours were related to increased UDP-GT levels and disturbances of the T3 and T4 metabolism, common findings specific to rodents.

There was no evidence of teratogenicity in rats or rabbits. Slight, but reversible, decreases in sperm counts and mobility were noted in male rats. In female rats, silodosin was associated with alterations in the oestrus cycle at high doses, but not with infertility. Decreased fertility and implantation rates were also noted at >20 mg/kg/day in a study in which only males were treated with silodosin after a 2-week drug-free period. In dogs, delayed maturation of genital organs (13 week study) was noted at 50mg/kg/day and decreased spermatogenesis was observed at doses approximately 5 times higher than the maximum recommended human dose at 13 weeks. This finding was not seen in 52-week dog study.

In vitro and *in vivo* phototoxicity studies suggest that silodosin may have the ability to increase sensitivity to sunlight.

Muscular damage of silodosin for injection was more severe than physiological saline but less severe than damage from 0.425% and 1.7% acetic acid solution (positive control).

All toxicology findings have been adequately reflected in the SmPC and risk management programme for silodosin.

2.4 Clinical aspects

Introduction

Silodosin has been developed for the treatment of benign prostatic hyperplasia (BPH). It is an α1-adrenoreceptor antagonist that selectively affects the prostate, the urethra, and the trigone of the urinary bladder relaxing smooth muscles in the lower urinary tract. Silodosin is intended to be administered to adult males at a dose of 8 mg daily. The 4 mg strength has also been developed for special populations (patients with moderate renal impairment).

The clinical development programme consisted of 36 studies.

The efficacy and safety of silodosin has been assessed in four controlled clinical studies: one Phase II study conducted in the United Stated (US), and three Phase III studies, two of which were conducted in the US and one in Europe. Additionally, the long-term efficacy of silodosin was evaluated in two open-label (OL) safety extension studies, one OL study conducted in the US (extension of studies SI04009 and SI04010) and one conducted in Europe (extension of study IT-CL 0215), as summarised in the table below.

Study ID	Design/ Posology	Duration	Primary Endpoint
US021-99	Parallel groups: Silodosin 4 mg QD (n=88) Silodosin 8 mg QD (n=90) Placebo (n=86)	• 4 weeks placebo run-in • 2 weeks dose adjustment • 6 weeks treatment	Change from baseline at week 8: overall AUA score and Qmax
SI04009	Parallel groups: Silodosin 8 mg QD (n=233) Placebo (n=228)	• 4 weeks placebo run-in • 12 weeks treatment • 40 weeks open label Extension (SI04011)	Change from baseline in total IPSS score at week 12
SI04010	Parallel groups: Silodosin 8 mg QD (n=233) Placebo (n=229)	• 4 weeks placebo run-in • 12 weeks treatment • 40 weeks open label Extension (SI04011)	Change from baseline in total IPSS score at week 12
IT-CL0215	Parallel groups: Silodosin 8 mg QD (n=381) Tamsulosin 0.4 mg QD (n=384) Placebo (n=190)	• 4 weeks placebo run-in • 12 weeks treatment • 40 weeks open label Extension	Change from baseline in total IPSS score at week 12

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Thirteen clinical pharmacology studies provided general pharmacokinetic information. Five studies investigated intrinsic factors affecting pharmacokinetics (including age, renal and liver dysfunction), five studies focused on pharmacokinetic interactions, one study was a QTc investigation, and one study investigated a pharmacodynamic drug-drug interaction. Four phase II/III studies provided pharmacokinetic information from 595 patients (85 from KMD-201, 9 from US021-99, 243 from SI04009 and 258 from KMD-305).

Several analytical methods were used during the various stages of development of the product. All of them have been sufficiently validated for selectivity (blank check and matrix effect), linearity, precision, accuracy, reproducibility, recovery and stability parameters.

Pharmacokinetic parameters were calculated by a non-compartmental analysis. In the food effect study (KDM-308), fasting/non-fasting ratio of Cmax and AUC and corresponding 90%CI were calculated using the standard methodology. The mixed model using log-transformed values of Cmax and AUC0-48 as the response variable, the presence or absence of food and period as fixed effect, and subject as random effect was applied.

- Absorption

- Bioavailability
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 administration over 4 h (KMD-308). The study also assessed the food effect after single oral doses of 4 mg.

Pharmacokinetic parameters of unchanged silodosin were as follows:

PK indices (mean ± SD)	Single oral administration 4 mg (fasting state)	Single IV administration 2 mg (fasting state)
Cmax:	27.986±9.555 ng/mL,	42.907±7.902 ng/mL
AUCinf:	133.7±58 ng/h/mL,	206.9±41 ng/h/mL
tmax:	1.36±1.12 h	4.00±0.00 h
t1/2:	4.714±3.710 h	3.614±1.718 h

The extent (mean ± SD) of bioavailability (F) was calculated as 32.2±11.4%.

An *in vitro* study using Caco-2 cells overexpressing P-gp was also performed to determine the involvement of P-gp in the membrane transport of silodosin. The membrane transport coefficient (Papp) of 14C-silodosin for B (basolateral) to A (apical) transport was 10.4 times higher than that for A to B, suggesting an involvement of an efflux transporter preferred direction in cellular membrane transport. Basal to apical transport was inhibited by verapamil, a well known inhibitor of P-gp. This information is adequately reflected in the SmPC.

- Bioequivalence
During the course of drug development clinical supplies of silodosin capsules have been produced by three distinct methods of manufacture. The first generation capsules were used in the early clinical studies (manufacturing method A). The second and third generation capsules (methods B and C) were used in phase II and phase III clinical studies. An active and placebo controlled phase III efficacy study (IT-CL-0215) was conducted with the final marketing product 8 mg capsule. Dose finding (US021-99) and the two placebo controlled studies (SI04009, SI04010) were conducted with a 4 mg final marketing formulation.

In vivo investigation of the bioequivalence of the 8 mg capsules and 4 mg capsules utilised in pivotal clinical trials was not performed. According to the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" CPMP/EWP/QWP/1401/98, silodosin capsules are considered highly water soluble, since the amount contained in the highest strength (8 mg) is dissolved in 250 mL

of each of three buffers at pH 1.2, 4.5 and 6.8 at 37°C, and >85% dissolves within 15 min. Therefore, a biowaiver to conduct a bioequivalence study with the 8 mg and 4 mg capsules is acceptable from the clinical point of view.

- Influence of food
In three studies (Studies 95283, UK01-97, KMD-308) the effect of food on the pharmacokinetics of silodosin was investigated. Food decreased Cmax by approximately 30%, delayed tmax by approximately 1 h, and had a negligible effect on the AUC. Silodosin is recommended to be taken with food in order to minimise the risk of orthostatic hypotension. This information is adequately reflected in the SmPC.

- Distribution

In healthy adult males the volume of distribution was 0.8 L/kg (49.5 L) after a single intravenous administration of a 2 mg of silodosin over a 4 h infusion (Study KMD-308).

Plasma protein binding

Plasma protein binding was evaluated in three studies (PK10153, DMPK2003-0053, DMPK2004-0033). The binding rate against human plasma protein was almost constant regardless of the concentration of 14C-silodosin added, and was between 94.6% and 95.8%. The binding to α1-acid glycoprotein was predominant (94.3 to 96.0%). The binding rate of the metabolites KMD 3213G and KMD 3293 against human plasma protein was 91.2% to 92.0% and 90.2% to 91.9%, respectively. Similarly to silodosin, binding to α1-acid glycoprotein appeared to be predominant for KMD 3213G and KMD 3293. Silodosin did not distribute to blood cells in the study assessing plasma-blood partition (PK10091).

- Elimination

Excretion

Results from a mass balance study (US012-99) in which 6 healthy male volunteers received a single dose of 8 mg of silodosin showed that the product was rapidly absorbed with tmax of 2.17 h. The AUC0-t of silodosin represented less than 10% of the total plasma radioactivity. The plasma concentration decreased with t½ of 12 h while the elimination half life of radioactivity in plasma was 125 h suggesting that silodosin undergoes extensive first pass and systemic metabolism and some of the metabolites have very long elimination half life. Radioactivities were excreted mainly in faeces; 55% of the dose was excreted in faeces by 144 h post-dose. Cumulative urinary excretion was 34% of total dose by 48 hours post-dose. In faeces, unchanged silodosin accounted for 28% and 15% of total faecal radioactivity and of total dose radioactivity, respectively. The urinary recovery of unchanged silodosin was less than 3% of the dose. A metabolite profiling was performed and two of the metabolites, KMD 3213G and KMD 3293, were determined as major contributors for the total circulating radioactivity.

Similarly, other single-dose oral administration studies (95283 and 98363) and the 7-day repeated-dose oral administration studies (95284 and 98364) showed that the urinary cumulative excretion rate of unchanged silodosin was less than 5%.

In study KMD-308 after intravenous administration of a 2 mg of silodosin over a 4 h infusion, the total body clearance was determined to be 2.8 mL/min/kg. In the same study, after oral administration of 4 mg silodosin the calculated total clearance was 9.5 mL/min/kg and 10.2 mL/min/kg under fasting and fed conditions, respectively. The clearance values were recalculated as L/h/kg in response to CHMP request. They ranged from 0.164 L/h/kg after the iv administration to 0.998 L/h/kg after the oral administration.

Metabolism

In vitro

A series of *in vitro* studies were performed in order to detect the metabolic pathway of silodosin (studies PK10104, PK-03-519, AE-3348, PK10126, KMD-OIR 001, DMPK 2003-0037). The major

metabolites observed after incubation with human hepatic cells was KMD 3213G and KMD 3293. While generation of KMD 3293 was also observed in rat, dog and monkey hepatic cells, KMD-3213G was generated in only an extremely small amount in the species other than humans. In addition to these metabolites, KMD 3295, KMD 3310 and KMD 3289 were observed in human hepatic cells, though their percentages of generation were very small. The generation of KMD 3213G was noted with UGT2B7, while both alcohol dehydrogenase and aldehyde dehydrogenase were assumed to be involved in generation of KMD 3293. Results revealed also that CYP3A4 played a predominant role (70%) in the oxidation and metabolism of silodosin in human hepatic microsomes. CYP2D6 (20%) and CYP1A2 (20%) also contributed to the metabolism of silodosin as shown by the decrease of metabolites after co-incubation with an enzyme-specific inhibitor. The CHMP has requested the applicant to discuss possible metabolic interactions and subsequent potential for drug-drug interactions of silodosin. In their response, the applicant has presented a detailed discussion on the metabolic pathways of silodosin. Moreover, a warning regarding the co-administration of silodosin with CYP3A4 inhibitors was added to the SmPC.

In vivo
In a mass balance study (US012-99), the major metabolites were KMD 3213G and KMD 3293 in plasma, KMD 3293, KMD 3310 and KMD 3213G in urine, and KMD 3293, KMD 3241, KMD 3295 and KMD 3289 in faeces.

- Inter-conversion

Silodosin exhibits chirality and the drug substance is the R-enantiomer. The potential for silodosin inter-conversion was discussed. The submitted results confirmed that no inter-conversion occurred in the clinical setting.

- Pharmacokinetics of metabolites

Less than 5% of silodosin is excreted unchanged in urine. Silodosin undergoes extensive first pass metabolism (absolute bioavailability 30%) and is metabolised extensively. Main metabolites are silodosin glucuronide (KMD 3213G) and KMD 3293. The exposure of KMD 3213G is 4-times higher than the exposure to unchanged silodosin. KMD 3213G is eliminated in urine with half-life of 15 to 20 h. KMD 3293 is also eliminated renally with half-life of 10 to 15 h. No accumulation of silodosin or KMD 3293 occurred after multiple dose administration, whereas the KMD 3213G exposure increased more than 2 fold after repeated administration. In early phase I studies, the pharmacokinetic parameters of metabolites KMD 3241 and KMD 3289 were determined. Results from the mass balance study indicated that these metabolites accounted for less than 2% of total radioactivity.

- Dose proportionality and time dependencies

Dose proportionality and time dependencies were assessed in healthy volunteers including older subjects (50-70) in a number of single-dose studies 95283, 98363, KMD3213-UK01-97, and repeat-dose studies 95284, 98364, UK02-97, US011-98, KMD-207; while steady state PK parameters were assessed in studies SI06004, SI05008, and SI07004.
Dose linearity of silodosin has been shown over a dose range of 0.1 mg to 48 mg. After multiple-dose administration, steady state of silodosin was reached on day 3 and no accumulation of silodosin after multiple dose compared to a single dose administration occurred. The KMD 3213G metabolite exhibited 2-3 fold increase in systemic exposure after multiple dose administration. At steady state KMD 3213G reached exposure that was approximately 4.5-fold that of silodosin. Inter-individual variability for Cmax and AUC of silodosin in phase I studies ranged from 35% to 50%.

- Pharmacokinetics in target population

In phase III study SI04009 plasma levels of silodosin and its metabolites were monitored in 233 patients with BPH after first dose and following 4 weeks of therapy (8 mg once daily). Plasma samples were collected between 2 and 6 hours post-dose. Concentrations of silodosin, KMD 3213G and KMD 3293 are presented below:

Concentration Type	Visit	Statistic	Placebo	Silodosin/Metabolites
Silodosin	Week 0 (Post-Dose)	Mean (SD)	0.1 (1.48)	49.3 (32.16)
		SEM	0.10	2.13
		CV (%)	1010.0	65.2
		Min, Max	0.0, 15.7	0.0, 285.0
		n	223	229
	Week 4	Mean (SD)	0.0 (0.69)	33.6 (26.52)
		SEM	0.05	1.85
		CV (%)	1469.7	78.8
		Min, Max	0.0, 10.1	0.0, 150.5
		n	216	205
KMD 3213G	Week 0 (Post-Dose)	Mean (SD)	0.1 (0.75)	38.1 (24.79)
		SEM	0.05	1.64
		CV (%)	1493.3	65.0
		Min, Max	0.0, 11.2	0.0, 155.5
		n	223	229
	Week 4	Mean (SD)	0.2 (2.20)	81.5 (51.31)
		SEM	0.15	3.59
		CV (%)	1469.7	63.0
		Min, Max	0.0, 32.4	0.0, 269.5
		n	216	204
KMD 3293	Week 0 (Post-Dose)	Mean (SD)	0.1 (0.80)	26.4 (17.56)
		SEM	0.05	1.16
		CV (%)	969.6	66.4
		Min, Max	0.0, 8.5	0.0, 136.5
		n	223	229
	Week 4	Mean (SD)	0.0 (0.35)	28.5 (17.86)
		SEM	0.02	1.25
		CV (%)	1469.7	62.6
		Min, Max	0.0, 5.2	0.0, 98.3
		n	216	205

The data showed no significant accumulation of silodosin or metabolite KMD 3293 after four weeks of treatment, an observation that is congruent with the known half-life of these two moieties (approximately 11 hours). Some accumulation was observed for the silodosin glucuronide after multiple dosing, as expected based on its longer half-life (approximately 18 hours).

The pharmacokinetic analysis was also conducted in 2 phase II studies (US021-99, KMD-201) in 94 patients. In the study US021-99 the peak plasma concentrations of silodosin were reached 1 to 2 hours post-dose, and ranged between 5.29 ng/mL and 49.30 ng/mL, after 4 and 8 mg doses. The metabolites reached peak plasma levels 1.5 to 4 hours (KMD 3293) or 1.5 to 6 hours (KMD 3213G) post-dose. In a 4-week repeat-dose study KMD-201 silodosin plasma concentrations 4 to 6 h after administration of the last dose were similar in patients <65 years and >65 years irrespective of the dose administered.

Another study (IT-PK 0241) investigated pharmacokinetics of 8 mg once daily silodosin in healthy adult males (45-64 years) and in two groups of elderly men, 65 to 75 years of age and >75 years. Capsules containing 8 mg of silodosin were administered orally for 7 days 30 min after a standard breakfast. The levels of silodosin and its main metabolites at steady state were similar among subject with different ages: group A (65-75 years), group B (over 75 years) and group C (45-64 years). Population PK analysis indicated that steady-state concentrations would increase by approximately 1.2 times when age is increased by 10 years from 67 years. Therefore it can be concluded that exposure to silodosin and its metabolites is not expected to change significantly with age. This information is adequately reflected in the SmPC.

- Special populations

Impaired renal function

Two studies (KMD-309, IT-PK 0234) investigated the pharmacokinetics of silodosin and its metabolites in patients with varying degrees of renal impairment (from mild to severe) and healthy

controls after a single oral dose. In the first study the dose of 4 mg was administered to 13 participants under fasting conditions (6 patients and 7 controls), while in the second study most of the patients and healthy controls received 8 mg (n=17 and 8, respectively), while four patients with severe renal impairment were given 4 mg. The drug was administered after a standard breakfast. The results showed that systemic exposure to silodosin and KMD 3213G metabolite was increased 2-fold in patients with mild (50 ≤ CLCr ≤ 80 mL/min/1.73 m2) and moderate renal impairment (30 ≤ CLCr < 50 mL/min/1.73 m2) after a single dose administration. In patients with severe renal failure (CLCr < 30 mL/min/1.73 m2) dose-normalised Cmax and AUC were 2- to 4-fold higher than in healthy subjects. Population PK analysis (KMD-305) revealed that silodosin exposure is increased 1.2 times when serum creatinine is increased from 1.0 to 1.5 mg/dL.

The CHMP has asked the applicant to further discuss these findings. Following the discussion it was acknowledged that the 2-3 fold increase in exposure of silodosin seen in patients with renal failure might be caused by increased serum concentrations of the acid alpha 1-glycoprotein, a finding often encountered in the renally-impaired patients. Consequently, silodosin is not recommended in patients with severe renal failure and a starting dose of 4 mg in patients with moderate renal impairment is proposed. Based on the efficacy data (in placebo controlled studies 273 patients with mild renal impairment received silodosin) and safety data (no additional safety risks were identified), no dose reduction is required in the patients with mild renal impairment. This information is adequately reflected in the SmPC.

Impaired hepatic function

The study SI05010 investigated a single dose pharmacokinetics of silodosin in subjects with moderate liver dysfunction, and in healthy controls. The study was designed as a two-period crossover study, 9 healthy volunteers and 9 subjects with moderate liver impairment (Child-Pugh score 7-9) received 4 mg and 8 mg of silodosin after a standard breakfast in period 1 and 2. Dosing periods were separated by 7-14 days. The indocyanine green test was performed on all liver dysfunction subjects to qualitatively evaluate liver function.

Cmax and AUC values for total concentrations of all moieties were slightly lower for subjects with liver dysfunction compared with healthy controls (ratios of means 0.8 and 0.8, respectively), while Cmax and AUC values for unbound concentrations were slightly higher for silodosin (ratio of means 1.1, 1.2), and slightly lower for KMD 3213G (0.9, 0.5) and KMD 3293 (0.9, 0.8). Vd of total silodosin was 234.3 (71.4) L and 280.8 (40.1) L in control subjects for a dose of 4 mg and 8 mg; and 286.3(119.2) L and 447.5 (181.1) L in subjects with moderate liver failure for a dose of 4 mg and 8 mg, respectively. Total clearance was approximately 50% increased in patients with moderate liver failure. Relative to healthy controls renal clearance of unchanged silodosin as calculated from urinary data appeared larger in subjects with moderate liver dysfunction, 724.2 (188.0) mL/h versus 413.8 (230.0) mL/h.

The CHMP has asked the applicant to submit the individual Child-Pugh scores and laboratory test results in order to elucidate the reasons for the unexpected lower silodosin exposure observed in patients with moderate liver failure, as compared to healthy controls. The submitted data showed that one subject had Child-Pugh score 9, three subjects had score 8, and five additional subjects had the score 7 providing reassurance that the enrolled patients were representative of a population with impaired liver function. All patients had normal biochemistry values; except for the patient with Child-Pugh score 9, who had slightly decreased albumin levels. Most of the patients had clinical signs of liver failure including ascites and encephalopathy. It was therefore concluded that the unexpected lower silodosin exposure could be explained by an increased volume of distribution due to ascites. The Cmax and AUC of KMD 3213G was 1.5 to 2 fold lower in patients with hepatic impairment, indicating lower glucuronidation in subjects with liver impairment. These results are expected from the PK profile of silodosin. Since KMD 3213G is pharmacologically active and accounts for a part of pharmacological activity of silodosin, it is agreed that no dose reduction is needed in patients with moderate liver failure. This information is adequately reflected in the SmPC.

Gender, race and weight

Silodosin is indicated for the treatment of BPH. No PK studies have been conducted in women and this is acceptable.

No clinical studies were performed to specifically investigate the effect of race. However, a review of the pharmacokinetic data obtained in Caucasians and Japanese does not suggest a significant effect of race on the pharmacokinetics of silodosin or its main metabolites.

Population PK showed that silodosin exposure is expected to be increased by 1.2-times when weight is decreased by 10 kg (from 64 kg to 54 kg). Therefore it can be concluded that weight does not affect systemic exposure of silodosin in a clinically significant manner.

Children

No specific studies have been performed in children.

- Pharmacokinetic interaction studies

Five *in vivo* studies investigated effects of concomitant medication on silodosin and its main metabolites. Two studies were conducted with ketoconazole, an inhibitor of CYP3A4 (KMD-306-UK, SI06008), one study with diltiazem (IT-PK 02042), an inhibitor of CYP3A4 and P-gp and two studies assessed silodosin effect on the PK of digoxin (KMD 307, IT-PK 0263), a substrate of P-gp. Ketoconazole was found to cause a 3-fold increase in AUC and a 3-4-fold increase in Cmax of silodosin. AUC and Cmax of the metabolites were also increased but to a lesser extent. Yet, Kel of silodosin was only slightly reduced (-18%) by ketoconazole, and that of the metabolites was unchanged. Ketoconazole markedly reduced CL/F by about 65% and Vz/F by about 55%. Ditiazem, a moderate inhibitor of CYP3A4, increased AUC of silodosin by approximately 30% and decreased the drug's apparent clearance by 26%, while Cmax was not affected. Diltiazem increased also the exposure to metabolites KMD 3293 and KMD 3213G to a similar extent as the parent drug (32% and 39%, respectively). *In vitro* data generated using Caco-2 cell monolayers have shown that silodosin is a substrate for P-gp. In the 2 *in vivo* studies after administration of silodosin no changes in the digoxin pharmacokinetics at steady-state were observed. Overall results from these studies indicate that no dose reduction is needed when silodosin is co-administered with digoxin or diltiazem, however caution should be exercised when starting concomitant use of silodosin and antihypertensives. Silodosin should not be administered with potent CYP3A4 inhibitors since its exposure was increased by 3-fold after co-administration with ketoconazole. Information on potential for drug-drug interactions is adequately reflected in the SmPC.

- Pharmacokinetics using human biomaterials

Several *in vitro* studies were performed in order to examine the potential for pharmacokinetic interactions of silodosin and its metabolites. Studies PK10049 and KMD 3213-IT-PK 0239 evaluated the effects of silodosin, KMD 3293 and KMD 3213G on the metabolic activities of CYP isoforms in human liver microsomes. In Study PK 03-010 possible effects of concomitant drugs (clarithromycin, cimetidine, fluvoxamine, diltiazem, nifedipine, verapamil, glibenclamide, prednisolone, simvastatin, triazolam and ketokonazole as positive control) on CYP3A4-mediated metabolism of silodosin to KMD-3241 were studied using CYP3A4-expressing microsomes, while study ZXA0002 investigated the potential of silodosin and its metabolites KMD 3213G and KMD 3293 to induce CYP1A2 and CYP3A4/5 in cryopreserved human hepatocytes. The results of *in vitro* studies suggested that silodosin and its metabolites KMD 3213G and KMD 3293 do not inhibit CYP450 activity significantly. There is no indication for the induction of either CYP1A2 or CYP3A4/5 by silodosin and its two main metabolites.

Pharmacodynamics

- Mechanism of action and primary pharmacology

In the absence of a robust biomarker predictive of therapeutic response no specific pharmacodynamic were performed. In non-clinical studies, silodosin was shown to block the sympathetic nervous system via the α1A-AR subtype distributed in the prostate, urethra and trigone of the bladder to relieve tension of the smooth muscles of lower urinary tract tissues. This reaction decreases urethral pressure, thereby improving the symptoms associated with benign prostatic hyperplasia.

The preliminary effects of silodosin on symptoms of benign prostatic hyperplasia were assessed in three phase I/II clinical studies conducted in Japanese patients (KMD-201, KMD-202, KMD-206). Moreover, a phase III confirmatory study (KMD-303) conducted in Japan was assigned as a supportive pharmacodynamic study for the European submission.

The brief outline of the early studies is presented in the table.

Study ID	Study design	Test products	Study objectives and end-points	Study dura-tion	N	Inclusion criteria	Outcomes
KMD -201	Early Phase II randomised, double blind, parallel group	Silodosin 0.1 mg, 1 mg, 2 mg PO, BID	Dose-finding Global improvement rating (1' endpoint) Subjective and objective improvement rating, Qmax (2' endpoints)	4 wk	S 0.2 mg =47 S 2 mg =49 S 4 mg =45 Total=141	Dysuria, BPH diagnosed by rectal exam or echography, total IPSS score ≥8, maximum flow rate (Qmax) <15 mL/sec, residual urine volume >50 mL, prostate volume >20 mL, QOL ≥2	No significant dose-related improvement
KMD -202	Late phase II randomised, parallel groups, double-blind, placebo controlled	Silodosin 2 mg, 4 mg Placebo PO, BID	To test superiority vs. placebo Subjective improvement rating in the IPSS (1') Qmax, QOL in the IPSS in the full analysis set (FAS)	4 wk	S (4 mg)=90 S (8 mg)=92 P=89 Total=271	Similar to study KDM-201	Improvement on IPSS for both S arms; based on QOL a dose-response was seen for S arms
KMD -206	Phase II not controlled	Silodosin 4 mg PO, BID	To investigate the effects on voiding mechanism and safety of 4 mg BID Improvement in the IPSS score of subjective symptoms (1') QOL, Qmax, overall improvement and the total IPSS (2')	4 wk	12	Similar to study KDM-201	50% of patients reported symptom improvement

Study KMD-303 was a randomised, double-blind, parallel group controlled study comparing 4 mg silodosin BID (n=176), 0.2 mg tamsulosin (n=192) and placebo (n=89) over 12 weeks. Patients with micturition disorder associated with BPH who met the following inclusion criteria were enrolled to the study: total IPSS score ≥8, Qmax <15 mL/sec, residual urine volume >100mL, voiding volume <100mL, prostate volume in ultrasound >20 mL, QOL ≥3. Eligible patients were 50 years and older.
Primary efficacy endpoint was the change in the total score of IPSS at week 12 in the full analysis set. Various secondary outcome measures, including change in Qmax, were also determined. The superiority of silodosin to placebo was confirmed ($p<0.001$) and the non-inferiority of silodosin to tamsulosin was also confirmed ($p<0.001$) for the primary endpoint. No difference between the

treatment groups for the maximum flow rate was observed, while silodosin showed superiority to placebo in the IPSS obstructive and irritative symptom scores ($p<0.001$ and $p=0.006$, respectively). Slightly more patients in the silodosin arm discontinued study prematurely (22 vs. 14 in tamsulosin and 8 in placebo group). The incidence of adverse drug reactions was also slightly higher in the silodosin group (69.7%, 47.4% and 36.4% in the silodosin, tamsulosin and placebo group). The most common adverse event in the silodosin group was ejaculation disorder with a frequency of 22%, whereas in the tamsulosin group it was reported in 1.6% of patients. Adverse events related to the orthostatic hypotension occurred with a frequency of 5.7%, 6.8% and 2.2% in the silodosin, tamsulosin and placebo groups, respectively.

- Secondary pharmacology

Silodosin effect on the prolongation of QT interval was investigated in the study SI05014. This was randomised, placebo controlled, four-arm parallel group investigation with 400 mg moxifloxacin as an active control (N=47). Silodosin was administered for 5 days at two different dose levels (8 mg and 24 mg) to healthy male subjects aged 18-45 (N=48 and 45, respectively). A total of 50 ECGs per subject were planned to be analysed at baseline (5 ECGs x 10 time points). These baseline ECGs were used to construct an individually corrected QT value (QTcI) in addition to the Bazett's and Fridericia's corrections. For the proposed therapeutic dose 8 mg of silodosin, the upper 90%CI for the difference was less than 10 msec throughout 24 h post dose. Mean change in QT interval was slightly higher for silodosin 24 mg arm, but at all time points upper 90%CI was less than 20 msec, regardless of correction. It was therefore concluded that no significant changes in QT interval were observed compared to placebo. This information is adequately reflected in the SmPC.

- Relationship between plasma concentration and effect

In the absence of a robust biomarker, no rigorous concentration-response investigations in humans have been performed with silodosin to investigate PK/PD relationship. The PK of silodosin has been sufficiently investigated in phase I studies, therefore further studies on PK/PD relationship are not required.

- Pharmacodynamic interactions with other medicinal product or substances

Another pharmacodynamic study (SI06002) examined interaction with PDE5 inhibitors sildenafil and tadalafil. The study was primarily designed to evaluate the effects on orthostatic blood pressure following co-administration of a single dose of 100 mg sildenafil, 20 mg tadalafil or placebo with 8 mg silodosin at steady state. It was an open-label, randomised, placebo-controlled, crossover study in 22 healthy male subjects of 45 years of age and older, including 6 subjects 65 years of age or older. Subjects received 8 mg silodosin daily for 21 days, representing three consecutive 7-day periods. At the end of each of these periods (days 7, 14, and 21), the subject was confined to the clinic for approximately 12 hours during which a PDE5 inhibitor (100 mg sildenafil, 20 mg tadalafil) or placebo were administered in the morning and orthostatic blood pressure tests were performed at 0, 1, 2, 3, 4, 6, 8, and 12 hours later. No significant changes in blood pressure and heart rate occurred when silodosin was co-administered with PDE5 inhibitors at a maximum daily dose. This information is adequately reflected in the SmPC.

Clinical efficacy

The efficacy of silodosin has been assessed in four controlled clinical studies: one Phase II study conducted in the United Stated (US), and three Phase III studies, two of which were conducted in the US and one in Europe. Additionally, the long-term efficacy of silodosin was evaluated in two open-label (OL) safety extension studies, one OL study conducted in the US (extension of studies SI04009 and SI04010) and one conducted in Europe (extension of study IT-CL 0215).

The three placebo-controlled Phase II/III studies conducted in the US enrolled 1,187 patients with BPH. In the European Phase III study KMD-3213-IT-CL 0215 a total of 977 patients with BPH were randomised, however, the final analysis excluded 22 subjects from one of the clinical sites due to inadequate adherence to Good Clinical Practice (GCP). The analyses presented further on are based on a total number of 955 patients enrolled in this study. Of the 1,187 patients enrolled in the US controlled studies, 661 continued into a 9-month open-label study (SI04011). Similarly, 500 of the 955

patients enrolled in the EU controlled study continued into a 9 month open-label phase (IT-CL 0215 OL extension phase), completing a 12 month treatment period.

- Dose response study

Study US021-99 was a multicentre, randomised, double-blind, parallel-group, placebo-controlled, dose adjustment study designed to evaluate the effective dosage and tolerability of silodosin in patients with BPH. It consisted of three periods: 4-week placebo lead-in period, 2-week dose-adjustment period, and 6-week stable dosing period. 264 patients were randomised to receive either placebo (N=86), silodosin 4 mg (N=88) or silodosin 8 mg (N=90) once daily.

The primary effectiveness parameters were change from baseline in the overall AUA Symptom Score, and change from baseline in Qmax. A number of secondary endpoints including proportion of responders at each visit during the double-blind treatment period were assessed. Responders were defined as patients who have a ≥30% improvement in Qmax and a ≥25% improvement in overall AUA Symptom Score. Safety was assessed by AEs, changes in physical examinations, monitoring of vital signs, 12-lead ECGs, orthostatic tests, and clinical laboratory tests.

Statistically significant results were obtained on both co-primary endpoints for the 8 mg silodosin arm compared with placebo (p=0.0018 and p=0.0174, respectively). The overall AUA Symptom Score improved also in 4 mg group (p=0.0355), while the change in Qmax was not statistically significant for the lower dose. The differences in responders rate were statistically significant between the 8 mg group and the placebo group for the AUA symptom index score responders, and between the 4 mg group and the placebo group for Qmax responders. Slightly more patients in the 8 mg silodosin arm experienced sexual dysfunction-type adverse events; retrograde ejaculation was more frequent in the 8 mg group (15.6%), as compared to the 4 mg group (11.4%), and placebo (0%). Similarly, ejaculation failure was seen in 11.1% patients in the 8 mg group, 9.1% patients in the 4 mg group, while it did not occur in the placebo group. Dizziness, headache and positive orthostatic test occurred more often in the 4 mg arm. Based on the results from this study the 8 mg dose was chosen for further development.

In the dose finding study the American Urological Association (AUA) Symptom Index was used for the primary efficacy assessment. This questionnaire is identical to the International Prostate Symptom Score (IPSS), used in the placebo controlled US studies (SI04009, SI04010) and in the active controlled EU study (IT-CL0215), except that it does not contain the quality of life question (8th question in the IPSS). Hence, AUA Bother Score and Quality of Life Questionnaire were used for secondary outcome assessment in the US021-99.

- Main study(ies)

Two placebo-controlled studies (SI04009 and SI04010, US studies) and one active-controlled study (IT-CL-0215, European study) investigated the effect of 8 mg silodosin daily on the symptoms of BPH after 12 weeks of treatment. Long term safety and efficacy data were collected up to 52 weeks of treatment in an open-label extension phase. The two US placebo-controlled studies (SI04009 and SI04010) had almost identical design. As mentioned above the Study IT-CL-0215 (a pivotal study for EU submission) was a three-arm study.

Unless specified otherwise the information presented in the following sections applies to all main studies.

METHODS

All main efficacy studies were conducted according to the classical randomised, double-blinded, controlled design. They were multicentre and of 12-week duration. In all main studies 4-week single-blind placebo run-in period preceded 12 weeks of therapy with silodosin, placebo or active control (study IT-CL-0215). Additionally, the study IT-CL-0215 used 14-day wash-out period prior to the placebo run-in. Study IT-CL-0215 was a placebo- and active-controlled (tamsulosin) and was conducted in 76 European sites located in Finland, France, Germany, Italy, the Netherlands, Poland, Romania, Russia, Spain, Ukraine, and the UK. At the end of all main studies patients had the option to enter a 40-week open-label extension.

Efficacy of silodosin was evaluated using the International Prostate Symptom Score (IPSS).

The seven questions of IPSS are identical to the questions of the American Urological Association Symptom Index (AUASI), and assess urinary symptoms occurring in the last month including incomplete emptying, frequency, intermittent stream, urgency, weak stream, straining, and nocturia. Questions 1-6 are graded using a 6-point scale with 0=”not at all” and 5=”almost always”, while for question 7 the descriptors vary from 0=”none” to 5=”5 or more times”. The total score is the sum of questions 1 through 7 with a maximum total score of 35 points. Sub-scores of irritative and obstructive symptoms is the sum of questions 2, 4, 7 and 1, 3, 5, 6, respectively. The symptom score is used to classify the severity of BPH symptoms as mild (score 0-7), moderate (8-19), and severe (20-35). Additionally, to the AUASI, the IPSS includes a disease-specific Quality of Life (QoL) question assessing the impact of urinary symptoms on the quality of life. The answers to this question are graded using a 7-point scale with 0=”delighted” and 6=”terrible” (Rosette et al. 2004, AUA guideline 2003).

The AUA symptom score was first published in 1992 (Barry et al.) and assessed the severity of symptoms during the last month. The score was not validated in men at similar age with and without BPH. It was not established whether the score had a discriminatory power from other lower urinary tract symptoms (LUTS). LUTS may reflect obstructive voiding (weak urine flow, hesitancy, straining, incomplete emptying) or bladder storage problems (frequency, urgency, nocturia). LUTS are often considered to be due to BPH, but are also common for detrusor overactivity and urodynamic stress incontinence. However, from the existing questionnaires the IPSS has been most widely used, also during drug development and therefore enables an indirect comparison of the treatment effect with literature data.

Study Participants
The study population consisted of male subjects aged ≥ 50 years with benign prostatic hyperplasia. The inclusion criteria were an IPSS score ≥ 13 and presence of bladder outlet obstruction as defined by a Qmax between 4 and 15 mL/sec, with a minimum voided volume of ≥ 125.
Patients with post-void bladder residual volume greater than 250 mL determined by ultrasound, history of postural hypotension and relevant medical conditions (e.g. prostate or bladder cancer) or receiving medications which might have produced confounding effects including alpha-blockers and 5-alpha-reductase inhibitors were excluded. In addition, patients with marked placebo response, i.e. greater than 30% decrease on the IPSS, or 3 mL/sec increase in Qmax in the US studies and ≥25% decrease on the IPSS in the EU study during the 4-week, single-blind, placebo run-in were also excluded.

Treatments
All studies dosed silodosin at 8 mg (2 capsules of 4 mg in US studies, 1 capsule of 8 mg in EU study), placebo or active control once daily at breakfast in the US studies (SI04009 and SI04010) or after breakfast in the European study IT-CL-0215. The study IT-CL-0215 used tamsulosin 0.4 mg as active control.

Objectives
The primary objective in all three studies was to determine whether silodosin 8 mg given once daily for 12 weeks is superior to placebo for the relief of symptoms of BPH; the European study IT-CL-0215 evaluated also the non-inferiority of silodosin to tamsulosin 0.4 mg administered once daily.

The secondary objectives included further assessment of efficacy (see secondary endpoints), assessment of quality of life and safety evaluation.

Additionally, a pharmacokinetic analysis of silodosin and major metabolites (plasma concentrations) was conducted during the SI04009 study only (see section on pharmacokinetics).

Outcomes/endpoints
The primary endpoint was a change from baseline in the total score of IPSS (Questions 1-7 referring to symptoms).

The secondary outcomes of the studies were:
• a baseline to endpoint change in the maximum urine flow rate (Qmax), and
• irritative and obstructive symptoms subscales of the IPSS and QOL due to urinary symptoms (question 8 of the IPSS),
• the safety of silodosin compared to placebo using an evaluation of adverse events, vital signs (including orthostatic test), ECGs, clinical laboratory tests, and physical exams.

Additional secondary endpoints in the IT-CL 0215 study included:
• percentage of respondents to IPSS, defined as percentage of patients with ≥ 25% decrease in IPSS compared to baseline,
• percentage of respondents to Qmax, defined as percentage of patients with ≥ 30% increase in Qmax compared to baseline.

The CHMP has considered the primary and secondary endpoints as appropriate given that the assessment of symptom severity is the most important outcome measure from the patient's perspective.

Sample size
In the US studies (SI04009, SI04010) the sample size considerations were based on a statistical estimation of the number of patients needed to achieve at least 90% power in the comparison of the silodosin treatment group to placebo for the primary efficacy endpoint, i.e. the difference of 1.54 of mean change from baseline in IPSS total score. The common standard deviation of change from baseline in IPSS total score was estimated as 5.2 based on previous studies. It was estimated that with 90% power using a two-sided t-test and Z=0.05 the difference between treatment groups could be detected with 240 patients (20% drop-out of 300 patients) completing the study in each treatment group.

In the European study (IT-CL-0215) the value of 2 was assumed as the minimum clinically significant difference to be used in sample size calculation for the comparison between active treatments and placebo (superiority), while 1.5 was the value considered as the maximum difference not clinically relevant for the comparison between two active treatments (non-inferiority). Taking into account the assumptions above, assuming a randomisation ratio silodosin: tamsulosin: placebo 2:2:1, a common standard deviation of 5.2 and a 0.025 one-sided significance level, a sample size of 260 subjects for each active treatment group and of 130 subjects for the placebo group has 90% power to reject the null hypothesis that the two active treatments are not equivalent, when the difference in mean change from baseline in IPSS total score is 1.5 or less. This sample size would be also sufficient to detect a difference of 2 in IPSS total symptom score between each active group and placebo using a two-sided test at 0.05 significance level and 90% power.

Randomisation
The US studies SI04009, SI04010 randomised patients in a 1:1 allocation scheme to receive either placebo or silodosin 8 mg, respectively. In the European study IT-CL-0215, patients were randomised according to a 2:2:1 scheme to receive either silodosin 8 mg, tamsulosin 0.4 mg or placebo. A randomisation schedule was produced using a block size of 5 to achieve the 2:2:1 ratio. The subject randomisation codes were to be allocated sequentially in the order in which subjects were randomised.

A number of randomisation irregularities were noted in the US studies including the allocation of the same treatment pack to two patients in one of the centres due to a transcription error. They were deemed not to have had an important impact on the results.

Blinding (masking)
All main studies were double-blind with blinding maintained throughout by use of identical medication packaging and a placebo that matched active treatment in size and external appearance. In the study IT-CL-0215 the blinding procedures included over-encapsulation of tamsulosin with the same capsules used for silodosin and placebo; double blind labelling with the subject randomisation number and a unique code identifying the global batch which maintained blinding of the study

medication. Dissolution study results presented in response to the CHMP request demonstrated that the over-encapsulation of tamsulosin did not affect the bioavailability of the drug. All studies used a statistical analysis plan that was approved before the study blind was broken. Any additional analyses that were implemented after the blind was broken were clearly described as post-hoc in the clinical study reports.

Statistical methods

For all main studies Intent-to-treat and modified ITT analyses included all randomised patients who received at least one dose of double blind study medication and had the IPSS assessment either at baseline in the US studies SI04009, SI04010, or both at baseline and at least one post-baseline visit (EU Study IT-CL-0215). In the EU study the PP (per protocol) population was defined as all patients in the ITT population without any major protocol violations. The primary efficacy endpoint in this study was analysed for both the ITT and the PP populations; the primary population for the primary efficacy variable was stated to be the PP population for the non-inferiority analysis and the ITT for the superiority comparisons.

The analysis of the primary efficacy variable was planned using an analysis of covariance (ANCOVA) with centre and treatment as effects and the baseline value as covariate. In the US studies SI04009, SI04010 the pooling algorithm would not apply and the centre effect would be removed from the analysis model if more than 10% or more than 5 centres were small. No centre effect on the study results was observed in the post-hoc analyses submitted at the request of the CHMP providing reassurance on the consistency and robustness of pooled results. Hypotheses were tested at the two-sided 5% level of significance. As only one comparison was required between silodosin and placebo in the US studies SI04009, SI04010, no adjustment for multiplicity was necessary. In the European study IT-CL-0215 the superiority of the active treatments, silodosin and tamsulosin versus placebo were tested first. If both were statistically established the superiority of silodosin compared with tamsulosin was tested subsequently. As this stepwise procedure was used no adjustments were made for multiple testing of the primary endpoint.

The 'last observation carried forward' approach (LOCF) was applied for the handling of missing data for the primary efficacy endpoint. A number of sensitivity analyses, including 'baseline observation carried forward' (BOCF), were conducted in order to confirm the robustness of the results of the analysis of the LOCF dataset in the US studies SI04009, SI04010.

In the US studies subgroup analyses were pre-defined by race and by geriatric status. A number of post-hoc analyses were carried out including an analysis of subgroups based on baseline creatinine clearance.

In general, the statistical methods used for the analysis of the primary efficacy endpoint were considered to be appropriate.

RESULTS

Participant flow

The subject disposition including patients who were randomised and completed or withdrew from the studies is presented below.

Study	No pts randomised	No of excluded following 4 week run-in	No pts completed	No pts discontinued
SI04009	Overall=461 Silodosin=233 Placebo=228	351	Overall=416 Silodosin=202 Placebo=214	Overall=45 Silodosin=31 Placebo=14
SI04010	Overall=462 Silodosin=233 Placebo=229	264	Overall=416 Silodosin=211 Placebo=205	Overall=46 Silodosin=22 Placebo=24
IT-CL-0215	Overall=955 Silodosin=381 Tamsulosin=384 Placebo=190	149	Overall=892 Silodosin=356 Tamsulosin=364 Placebo=172	Overall=63 Silodosin=25 Tamsulosin=20 Placebo=18

A total of 351 patients in the study SI04009, 264 in the study SI04010 and 149 in the EU study IT-CL-0215 were not randomised following the placebo run-in.

Conduct of the study
In the IT-CL-0215 study subjects from one of the centres were excluded from the statistical analysis following concerns regarding the GCP compliance of the site. Other most frequently reported violations that resulted in the exclusion of subjects from the PP population were a major violation of the IPSS questionnaire (missing or invalid IPSS total score at baseline or at week 12) and major violation of compliance (overall compliance during the double blind treatment period or at the last visit week 12 outside 80-120%). Three, four, and two patients in the silodosin, tamsulosin and placebo arm received prohibited concomitant medications. Minor amendments were made to the US study protocols SI04009 and SI04010. They were reviewed and approved by an independent ethics committee prior to implementation. The protocol violations were considered to have not affected the statistical analysis.

Baseline data
US studies SI04009 and SI04010: Demographic characteristics, general and urological medical history were similar for the treatment arms in both studies. Mean age was 64 and 65 years in the SI04009 and SI04010, respectively. In study SI04009, 195 (42.3%) were older than 65 years and 52 (11.3%) were older than 75 years. Approximately 87.6% of subjects were Caucasian, 6.3% Hispanic 3.7% African American and 1.7% Asian. In study SI04010, 220 (47.6%) were older than 65 years and 63 (13.6%) were older than 75 years. Approximately 90.9% of subjects were Caucasian, 4.1% African American, 3.5% Hispanic and 0.6% Asian.

EU study IT-CL-0215: Baseline demographic characteristics, medical history and efficacy variables were similar for the treatment groups. Mean age was 66 years, mean weight 80 kg, mean height 173 cm. All subjects enrolled in this study were Caucasian therefore the CHMP has requested the applicant to discuss generalisability of results to non-Caucasian patients. In their response the applicant has provided reassurance that results obtained in EU study could be extrapolated to other ethnic groups as PK studies did not suggest any meaningful differences between races in the pharmacokinetics of silodosin, no clinically meaningful treatment differences were observed between the races on any efficacy parameter in the US studies and data available from Asian patients suggested similar efficacy.

Numbers analysed
In the US studies (SI04009, SI04010) efficacy assessment was planned to be performed using the following patient populations:
• Intent-to-treat (ITT) population – all randomised patients who provided data for the primary efficacy variable at baseline; patients were included ‘as randomised’,
• Modified Intent-to-Treat (mITT) population – all randomised patients who provided data for the primary efficacy variable at baseline; patients were included ‘as treated’.

	Analysis populations	Silodosin n (%)	Placebo n (%)
SI04009	Safety analysis	233 (100%)	228 (100%)
	Intent-to-treat analysis	233 (100%)	228 (100%)
	mITT	233 (100%)	228 (100%)

	Analysis populations, n (%)	Silodosin	Placebo
SI04010	Safety analysis	233 (100%)	229 (100%)
	Intent-to-treat analysis	233 (100%)	229 (100%)
	mITT	233 (100%)	229 (100%)

In the European study IT-CL-0215 the primary populations for the analysis of the primary efficacy variable was the PP population for the non-inferiority analysis (silodosin vs tamsulosin) and the ITT population for the superiority analyses (silodosin vs placebo, tamsulosin vs placebo and, if applicable, silodosin vs. tamsulosin).

	Analysis populations	Silodosin n (%)	Tamsulosin n (%)	Placebo n (%)
IT-CL-0215	Safety analysis	381 (100%)	384 (100%)	190 (100%)
	Intent-to-treat analysis	371 (97.4%)	376 (97.9%)	185 (97.4%)
	Per-protocol Analysis	346 (90.8%)	347 (90.4%)	168 (88.4%)

In the EU study the ITT population represented a 'modified' ITT population as 23 randomised patients without post baseline IPSS assessment have been excluded. The additional analysis presented in the response to the CHMP request which included all randomised patients confirmed that this modification had no impact on results of superiority and non-inferiority analyses.

Outcomes and estimation

US studies SI04009 and SI04010:
Mean changes from baseline in the primary efficacy parameter (IPSS total score) are presented below (mITT).

IPPS total score results vs. placebo

Study	Treatment Arm	N	IPSS Total Score		
			Baseline Value	Change from Baseline	Difference from Placebo
SI04009	Silodosin 8 mg QD	233	22 ± 5	-6.5	P< 0.001
	Placebo	228	21 ± 5	-3.6	
SI04010	Silodosin 8 mg QD	233	21 ± 5	-6.3	P< 0.001
	Placebo	229	21 ± 5	-3.4	

At the primary endpoint, silodosin was significantly superior to placebo after 12 weeks of treatment. The treatment effect was seen already after 1 week of therapy and change in the IPSS score compared with placebo was maintained over the 12-week treatment period. Following the request of the CHMP the applicant has provided the analysis of the primary efficacy variable focusing on the estimated treatment differences from the ANCOVA with the associated 95% confidence intervals and results of the analysis of the primary endpoints for the evaluable patient population. The findings across the two studies and between evaluable and mITT populations were similar, i.e. silodosin vs. placebo -2.8 in study SI04009 and -2.9 in study SI04010, respectively.

EU study IT-CL-0215:
Primary efficacy parameter (IPSS total score)

- Treatment with silodosin was superior to placebo with respect to the change from baseline to week 12 in the total IPSS score in both the ITT and the PP populations.
- Treatment with silodosin was non-inferior to treatment with tamsulosin with respect to the change from baseline to week 12 in the total IPSS score in both the ITT and the PP populations.
- Treatment effect with silodosin was greater than with tamsulosin, but this difference was not statistically significant.

Final analysis excluding subjects enrolled at site 068	Silodosin 8 mg	Tamsulosin 0.4 mg	Placebo
- ITT population	N=371	N=376	N=185
Baseline (mean ± SD)	19 ± 4	19 ± 4	19 ± 4
Change from baseline to endpoint (adjusted means)	-7.0	-6.7	-4.7
Difference active - placebo (95% CI)	-2.3 (-3.2. -1.4)[1]	-2.0 (-2.9, -1.1)[1]	
Difference tamsulosin-silodosin (95% CI)	0.3 (-0.4, 1.0)[2]		
- PP population	N=346	N=347	N=168
Baseline (mean ± SD)	19 ± 4	19 ± 4	19 ± 4
Change from baseline to Week 12 (adjusted means)	-7.0	-6.7	-4.8
Difference active - placebo (95% CI)	-2.2 (-3.2. -1.3)[1]	-1.9 (-2.8, -0.9)[1]	
Difference tamsulosin-silodosin (95% CI)	0.4 (-0.4, 1.1)[2]		

[1] p< 0.001 vs placebo
[2] Non-inferiority

Ancillary analyses

The results of evaluation of several secondary variables are presented in the tables.

	***Study SI04009* Outcomes**	
Secondary/ancillary endpoints	Change from baseline at week 12	Silodosin 8 mg vs. Placebo at week 12 (95% CI)
IPSS irritative symptoms	Silodosin 8 mg (-2.3) Placebo (-1.4)	-0.9 (-1.37;-0.39)
IPSS obstructive symptoms	Silodosin 8 mg (-4.2) Placebo (-2.2)	-1.9 (-2.61;-1.23)
Change in Qmax	Silodosin 8 mg (2.2) Placebo (1.2)	1.0 (0.30;1.76)

	***Study SI04010* Outcomes**	
Secondary/ancillary endpoints	Change from baseline at week 12	Silodosin 8 mg vs. Placebo at week 12 (95% CI)
IPSS irritative symptoms	Silodosin 8 mg (-2.4) Placebo (-1.3)	-1.0 (-1.52; -0.56)
IPSS obstructive symptoms	Silodosin 8 mg (-3.9) Placebo (-2.1)	-1.8 (-2.53;-1.11)
Change in Qmax	Silodosin 8 mg (2.9) Placebo (1.9)	0.9 (0.03;1.70)

Results for secondary variables were consistent across the US studies. Additionally, statistically significant differences vs. placebo (as measured by a post-hoc investigation using the Cochran-Mantel-Haenszel test) were observed on Quality of life outcomes at all visits in study SI04010 and at week 1, 2, and 4 in study SI04009

	***Study IT-CL-0215* Outcomes**	
Secondary/ancillary endpoints	Change from baseline to endpoint	Difference silodosin-placebo at week 12 (95% CI)
IPSS irritative symptoms	Silodosin 8 mg (-2.5) Tamsulosin 0.4 mg (-2.4) Placebo (-1.8)	-0.7 (-1.1;-0.2)
IPSS obstructive symptoms	Silodosin 8 mg (-4.5) Tamsulosin 0.4 mg (-4.2) Placebo (-2.9)	-1.7 (-2.2;-1.1)
Change in Quality of life	Silodosin 8 mg (-1.1) Tamsulosin 0.4 mg (-1.1) Placebo (-0.8)	-0.3 (-0.5;-0.1)
Change in Qmax	Silodosin 8 mg (3.8) Tamsulosin 0.4 mg (3.5) Placebo (2.9)	0.84 (-0.13;1.81)

In the EU study results for secondary variables were consistent across treatment groups and were similar to those observed in the US studies except for Qmax. The percentage of responders on IPSS (≥25% decrease) was 66.8%, 65.4% and 50.8% in the silodosin, tamsulosin and placebo group, respectively, and was statistically significant vs. placebo ($p<0.001$). The percentage of responders on Qmax (≥30% increase) was 46.6%, 46.5% and 40.5% in the silodosin, tamsulosin and placebo group, respectively, without significant differences between the treatment groups ($p>0.1$).

- Analysis performed across trials (pooled analyses and meta-analysis)

Three US studies were included in the integrated summary of efficacy: one phase II study (US021-99) and two phase III studies (SI04009 and SI04010). The integration was performed with two data groups that reflect the differences in study design. The first integrated group included all three studies. The second integrated group included only the two placebo-controlled US phase III studies. Data analysis was performed on the mITT and evaluable population.

An integrated analysis of efficacy from the phase II and phase III studies revealed consistent and statistically significant results on the primary and secondary endpoints. The difference in the mean change from baseline between the silodosin and placebo arms was -2.8 with the lower 95%CI of -2.0. Silodosin's effect on symptoms of BPH as measured by a change from baseline in the IPSS total score exceeded that of placebo in a statistically significant manner ($p<0.0001$). The mean change in the total IPSS score was -6.4, versus -3.6 for placebo (all US studies). Statistically significant effect between the placebo and silodosin was revealed already after approximately 0.5 week of therapy with reductions in the IPSS scores of -4.2 versus -2.3 for placebo ($p<0.0001$) in phase III studies.

In phase III studies, silodosin's effect on irritative and obstructive symptoms of BPH as measured by a change from baseline in the subscale scores exceeded that of placebo in a statistically significant manner ($p<0.0001$). The mean change in the irritative score was -2.3 versus -1.4 for placebo, and in the obstructive score -4.0 versus -2.1 for placebo. Similarly, silodosin effect on Qmax was significantly superior to that of placebo ($p=0.0007$). The mean change in Qmax was 2.6 mL/sec versus 1.5 mL/sec for placebo. Similar onset of effect (2-6 hours post first dose) as that noted in the IPSS and subscales scores was observed for the Qmax.

The integrated analysis did not identify any age, race or renal function related differences in the efficacy. For the first integrated group (all US studies) 7.2% patients on silodosin arm and 1.9% patients on placebo arm discontinued the study due to adverse event.

Additional analyses were submitted following the CHMP request:
1. Post-hoc responder analysis including placebo responders in the run-in period; responders were defined as subjects showing a decrease in the total IPSS score ≥25% as compared to baseline.

In the European study IT-CL-0215 149 patients who entered placebo run-in were excluded from randomisation. For the post hoc analysis, 31 additional subjects were included and randomly assigned

to one of the three treatment arms. The 118 patients who were not included in the post-hoc analysis did not meet the inclusion criteria, suffered from adverse events, voluntarily withdrew from the study, were lost to follow-up or discontinued the treatment upon the investigator recommendation.
In the US studies 351 patients in the study SI04009 and 264 in the study SI04010 were not randomised following the placebo run-in; 125 out of 351 and 106 out of 264 patients were included in the post-hoc analysis. The reasons for non randomising remaining patients were similar to those in the European study. This was accepted by the CHMP.

In the EU study IT-CL0215, the inclusion of placebo-responders in the post-hoc analysis did not change the original conclusions of the study on efficacy. Also in the post-hoc analysis responder rates were significantly higher in the silodosin than in the placebo arm.

Study IT-CL 0215: Original and post-hoc responder analysis

	Silodosin No. responders/total (%)	Tamsulosin No. responders/total (%)	Placebo No. responders/total (%)
Original analysis (ITT)	248/371 (66.8%) P < 0.001 vs. placebo	246/376 (65.4%) P < 0.001 vs. placebo	94/185 (50.8%)
Post-hoc analysis	260/383 (67.9%) P < 0.001 vs. placebo	259/389 (66.6%) P < 0.001 vs. placebo	101/192 (52.6%)

Similar findings were observed in the US studies; the inclusion of placebo-responders in the run-in period, according to the IPSS data, did not change the efficacy conclusions of silodosin superiority vs. placebo.

Study SI04009: Post-hoc responder analyses

	Silodosin No. responders/total (%)	Placebo No. responders/total (%)
mITT	123/233 (52.8%) P < 0.0001 vs. placebo	72/228 (31.6%)
Including placebo-responders during the run-in period	185/295 (62.7%) P < 0.0001 vs. placebo	135/291 (46.4%)

Study SI04010: Post-hoc responder analyses

	Silodosin No. responder/total (%)	Placebo No. responder/total (%)
mITT	125/233 (53.6%) P < 0.0001 vs. placebo	75/229 (32.8%)
Including placebo-responders during the run-in period	178/286 (62.2%) P < 0.0001 vs. placebo	128/282 (45.4%)

2. Subgroup analysis in patients with moderate (IPSS<20) and severe symptoms (IPSS≥20)

Post-hoc subgroup analyses have been conducted, separately in patients with moderate or severe symptoms (IPSS total score < 20 or ≥ 20, respectively) to evaluate whether silodosin is effective also in patients with the moderate condition.

The results from the European study are presented in the tables.

Study IT-CL 0215: Post-hoc subgroup analyses in patients with moderate and severe symptoms (ITT population)

	Baseline IPSS < 20			Baseline IPSS ≥ 20		
	Silodosin (N=223)	Tamsulosin (N=224)	Placebo (N=103)	Silodosin (N=148)	Tamsulosin (N=152)	Placebo (N=82)
Baseline value (Mean ± SD)	16.3 ± 1.91	15.8 ± 1.81	16.2 ± 1.98	23.3 ± 3.23	23.3 ± 2.92	23.1 ± 3.27
Change from baseline (adjusted means)	-5.8	-5.4	-3.9	-8.7	-8.5	-5.8
Difference active-placebo (95% CI)	-1.9 (-3.0, -0.8) p< 0.001 vs. placebo	-1.5 (-2.6, -0.4) p 0.009 vs. placebo		-3.0 (-4.5, -1.4) p< 0.001 vs. placebo	-2.7 (-4.2, -1.2) p< 0.001 vs. placebo	

Study IT-CL 0215: Post-hoc subgroup analyses in patients with moderate and severe symptoms (PP population)

	Baseline IPSS < 20			Baseline IPSS ≥ 20		
	Silodosin (N=208)	Tamsulosin (N=208)	Placebo (N=96)	Silodosin (N=138)	Tamsulosin (N=139)	Placebo (N=72)
Baseline value (Mean ± SD)	16.3 ± 1.92	15.8 ± 1.78	16.3 ± 1.97	23.4 ± 3.26	23.3 ± 2.95	23.0 ± 2.95
Change from baseline (adjusted means)	-5.9	-5.3	-3.9	-8.7	-8.6	-6.2
Difference active-placebo (95% CI)	-2.0 (-3.1, -0.9) p< 0.001 vs. placebo	-1.5 (-2.6, -0.3) p 0.013 vs. placebo		-2.6 (-4.2, -1.0) p< 0.002 vs. placebo	-2.4 (-4.0, -0.8) p< 0.004 vs. placebo	
Non inferiority between silodosin and tamsulosin (95% CI)		0.6 (-0.4, 1.5)			0.2 (-1.2, 1.5)	

Similar results were observed in both US studies; the difference between placebo and silodosin arm was statistically significant in patients with IPSS<20 and with IPSS≥20, with slightly more pronounced difference in patients with severe condition.

Additional analysis provided by the applicant confirmed that the treatment effect observed both in patients with moderate and severe condition was in the same order of magnitude as in the whole patient population.

- Clinical studies in special populations

No formal studies in special populations were conducted. Race, age and renal function were not found to be associated with the efficacy of silodosin in phase III studies based on subgroup analysis conducted for the US studies.

- Supportive study(ies)

Long-term safety and efficacy of silodosin was investigated in two open-label non-comparative studies. At the end of the US studies, SI04009 and SI04010, patients had an option to enter a 40-week open-label extension study (SI04011). Similarly, after the completion of the EU study IT-CL-0215 patients were enrolled into an open-label extension phase of the study that lasted 40 weeks. The primary objective in both studies was the safety of silodosin 8 mg given once daily for 40 weeks. The secondary objective was to evaluate the sustained efficacy of silodosin 8 mg given once daily for 40 weeks for the relief of the signs and symptoms of BPH as measured by the change in the IPSS score.
In addition, two long-term open-label studies (up to 52 weeks of treatment) had been conducted with the silodosin 4 mg bid for the submission in Japan. Study KMD-203 was an extension of the KMD-

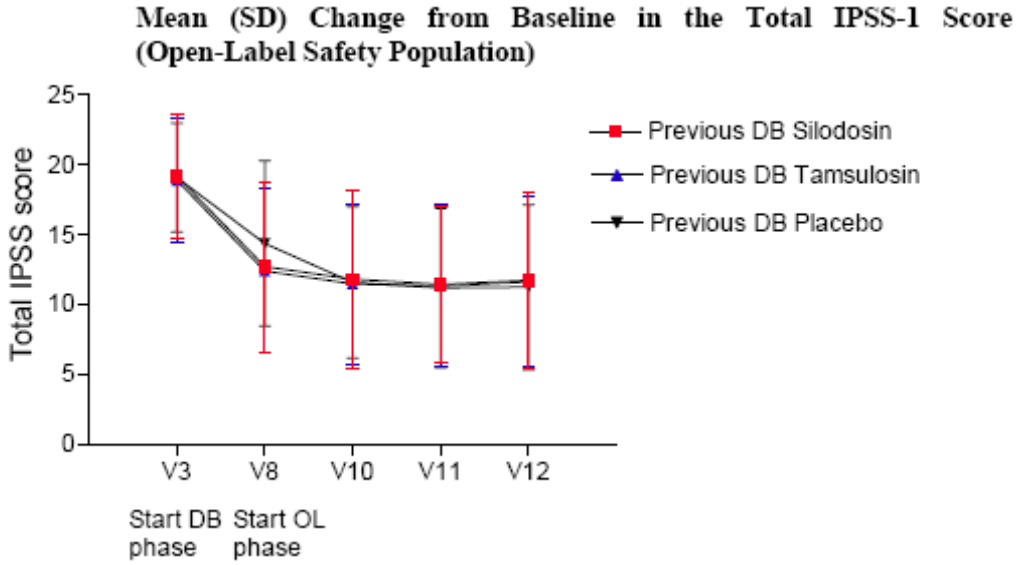
202 (see section on Pharmacodynamics). Thirty eight patients were enrolled in the 2 mg bid and 37 patients in the 4 mg bid group; 28 and 26 patients, respectively, completed the 52 week open label treatment. Due to a limited data set, efficacy results from this study are not discussed here in details. Study KMD-305 was initiated as an open label single arm (4 mg bid silodosin, 2 mg bid if not tolerated) treatment for 52 weeks.

SI04011
Visit 1 of this study occurred on the same day as the last visit of the double blind study. 661 men with signs and symptoms of BPH received silodosin 8 mg once daily at breakfast. ECGs were performed at Week 8 and 40, clinical laboratory tests and vital signs were performed at Week 8, 16 and 40 or discharge and a physical examination was performed at Week 40 or discharge. The IPSS was completed at Week 8 and 40 or discharge. Qmax was not assessed. A total of 661 patients were enrolled and 435 patients completed the study. The discontinuation rate was 34.2%. Ninety three patients (14.1%) withdrew due to adverse events, 58 (8.8%) due to lack of efficacy, 33 (5%) discontinued voluntarily and 21 (3.2%) were lost to follow-up.
Data showed that silodosin 8 mg once daily was effective in treating the symptoms of BPH for up to 9 months. Patients who had received placebo during the double blind study had larger decreases in the IPSS (-3.0±6.2) than patients who had received silodosin (-1.0±5.5). However, patients who had previously received silodosin continued to have meaningful effect on their BPH symptoms (IPSS score). Similar results were observed on the irritative and obstructive symptoms subscale.

In conclusion, patients who had received placebo in the double-blind phase, demonstrated improvement in the IPSS score at week 40 in the same order of magnitude as reported for silodosin arm at the end of 12-week treatment (i.e. end of the double blind phase).

IT-CL 0215 open label
After completion of the double-blind phase, a total of 54 centres enrolled 509 subjects into an open-label phase. Four visits were planned: at week 14, week 26, week 39 and week 52 (or earlier, in case of premature study termination) after double-blind period. The IPSS score, Qmax and ECG were assessed at Week 26, 39, and 52 at 2-6 hours after dosing. Overall 56 (11.2%) patients discontinued the study prematurely, including 19 (3.8%) due to adverse event. 9 subjects enrolled at one of the centres were excluded from the analysis due to an inadequate GCP compliance.

Change from baseline in the total IPSS score for the open-label safety population is summarised in the figure.



With reference to the IPSS total score, a marked reduction (-2.7±3.8) was observed at the first visit, after 14 weeks of an open-label treatment in subjects previously treated with placebo, while a smaller improvement was observed in subjects previously treated with silodosin or tamsulosin (-0.82±4.2 and

-0.83±3.8, respectively. The treatment effect was maintained up to 52 weeks. Similar findings were observed for the irritative and obstructive symptoms subscores. No clinically significant changes in Qmax measurements were observed in the open-label extension phase. No formal statistical analysis was performed.

Study KMD-305 enrolled 364 patients with signs and symptoms of BPH; inclusion/exclusion criteria and safety/efficacy assessment were similar to those in other studies. 260 patients completed an open-label 52-week treatment with 4 mg bid silodosin (if not tolerated 2 mg bid). Sixty three out of 104 patients discontinued due to adverse events. The reported change in the total IPSS score in numerical terms was similar to other studies (difference between weeks 12 and 52 – (-2.3)).

- Discussion on clinical efficacy

The efficacy of silodosin in the treatment of signs and symptoms of benign prostatic hyperplasia (BPH) was assessed in three main studies, two placebo-controlled US studies (SI04009, SI04010) and one active-controlled European study (IT-CL-0215). The CHMP has discussed the following efficacy aspects of the main studies:

a) Patients eligible at screening but demonstrating a significant placebo response after a 4-week placebo run-in period in phase III efficacy studies were excluded from randomisation. It is expected that the real treatment effect is smaller than reported for the enriched population in the efficacy studies.
Subsequently, the post-hoc analysis including also placebo responders from all three main studies was performed. Placebo responders were defined as subjects showing a decrease in the total IPSS score $\geq$25% in the run-in period. Additional 231 subjects in the US studies (125 and 106 in SI04009 and SI04010, respectively) and 31 in the European study were included in the post-hoc analysis. The reasons for not including the remaining subjects were discussed sufficiently by the applicant and acknowledged by the CHMP. The inclusion of placebo-responders in the analysis did not change the original conclusions of silodosin superiority versus placebo and non inferiority versus tamsulosin.

The applicant was also asked to justify why the cut-off $\geq$13 in the IPSS score was chosen for the inclusion in the phase III efficacy studies. Consequently, a post-hoc subgroup analysis has been conducted separately in patients with moderate or severe symptoms (IPSS total score < 20 or ≥ 20, respectively) in order to evaluate the efficacy of silodosin with respect to the severity of the condition. The results confirmed that the treatment effect observed both in patients with moderate and severe condition was in the same order of magnitude in as in the whole patient population.

b) The choice of the clinically important difference (-2 points) and the non-inferiority margin (-1.5 points) for study IT-CL-0215 has not been sufficiently justified either statistically or clinically. In addition, the clinical relevance of the treatment effect, namely -2.3 to -2.8 points change in the IPSS score on the silodosin arm compared to placebo should be established.
The literature data review submitted in response to the CHMP question demonstrated that the change in the IPSS score from baseline observed in silodosin arms was similar to those reported for other alpha-blockers providing justification for the non-inferiority margin. Similarly, the value of -2 points in the IPSS total score was considered as clinically relevant based upon previous clinical evidence showing that the minimum level of perception of improvement among men with moderate symptoms was set at -1.9 points. In addition, recently published meta-analysis on alpha-blockers also showed that the difference from placebo in American Urological Association Symptom Index/International Prostate Symptom Score was -1.92 points (95%CI: -2.71 to -1.14). Hence, it can be concluded that the treatment effect observed in the European study was similar to that observed in other trials with alpha-blocking agents.

c) Duration of the main efficacy studies was 12 weeks. No placebo controlled efficacy data are available beyond 12 weeks of treatment. The long term benefits of silodosin have not been established. No regulatory guideline exists on the investigation of products for the treatment of BPH. In previous clinical studies with drugs approved for BPH, the duration of main efficacy studies has been 12 weeks due to the fact that alpha-blocking agents show immediate therapeutic benefits.

Answering to the requests to provide data beyond 12 weeks of treatment, the applicant emphasised that the long-term benefits of silodosin have been shown in two open-label long-term studies in more than 900 patients treated for at least 6 months, and in more than 300 patients treated for 12 months. In both studies the treatment effect appeared soon after treatment initiation and was maintained over time. In acknowledging the response the CHMP underlined the limited validity related to an uncontrolled design of the open-label extension trials.

Clinical safety

A total of 36 clinical studies that provide safety data of silodosin were conducted in Europe, US and Japan involving both, healthy subjects or patients. More than 3000 subjects received at least one dose of the drug. Additional safety information is available from post-marketing experience in Japan from January 2006 until January 2008.

- Patient exposure

For the purpose of this application the overall silodosin safety population used to calculate frequencies of adverse events was integrated from the main controlled and open-label extension trials. A total of 1581 patients were exposed of which 961 (62.4%) were exposed for 6 months or more (438 patients <65 years, 523 patients >65 years) and 384 patients (24.9%) were exposed for 12 months or more (179 patients <65 years, 205 patients >65 years). 931 patients received daily doses of 8 mg silodosin and a total of 733 patients received placebo.

Demographic characteristics of the integrated safety population are shown below.

Safety population in controlled and open-label extension clinical trials and drug exposure

No. of patients	1,581
Caucasian	1,495 (94.6%)
Age (years) (mean ± SD, min-max)	64.5 ± 7.9 (44-87)
≥ 65 years	787 (49.8%)
≥ 75 years	177 (11.2%)
BMI (kg/m^2) 25-30 > 30	 849 (53.8%) 356 (22.5%)
IPSS score at baseline mild (0-7) moderate (8-19) severe (20-35) missing	 86 (5.5%) 827 (52.7%) 656 (41.8%) 12
History of cardiovascular disease - missing	844 (56.4%) 84
Diabetes	95 (6.3%)
Renal function (Cockroft-Gault formula) normal (> 80 ml/min) mild renal impairment (50-80 ml/min) moderate renal impairment (<50 to 30 ml/min) severe renal impairment (< 30 ml/min) missing information	 955 (64.6%) 487 (32.9%) 35 (2.4%) 1 (0.1%) 103
On antihypertensive treatment	500 (31.6%)
On PDE-5 inhibitors	114 (7.2%)
Duration of exposure (days) - mean ± SD - median - min-max - missing information	 224 ± 126 280 1, 471 43

Source: Silodosin Integrated Summary of Safety (2 September 2008)

Additionally, 88 patients were exposed to 4 mg of silodosin for 8 weeks in the dose-finding study US021-99.

A total of 873 Japanese patients with moderate to severe symptoms of BPH were exposed to silodosin doses ranging from 0.2 mg up to 8 mg/daily, with 650 patients administered 8 mg/daily (mean exposure 211 days ± 146 days).

Safety data collected in healthy volunteers or in special populations (elderly volunteers, renal insufficiency) from PK studies was not integrated, but described separately. Twenty-five clinical pharmacology studies were performed in a total of 595 subjects treated with silodosin at doses ranging from 0.1 mg to 48 mg.

Size of the safety population, both in terms of number of patients and duration of treatment, meets requirements in the ICH Topic E1 "Population Exposure: The Extent of Population Exposure to Assess Clinical Safety". Demographic characteristics of the integrated safety population are representative of the target patient population.

- Adverse events

In placebo controlled trials adverse reactions were observed in 268/931 (28.8%) patients treated with silodosin and 66/733 (9.0%) patients receiving placebo. Across all studies in the integrated safety population the most common (>1%) adverse reactions were retrograde ejaculation (23.6%), dizziness (2.1%), orthostatic hypotension (1.3%), nasal congestion (1.3%), headache (1.3%) and diarrhoea (1.0%). The adverse reactions observed in more than one patient in the overall safety population included testicular pain, urinary hesitation, urticaria, pruritus, arthralgia and blurred vision (N=2 each, 0.1%).

The occurrence of adverse reactions was not associated with the onset or duration of treatment. No remarkable age-related difference was seen in the incidence of adverse events considered related to study treatment with the exception of retrograde ejaculation which was observed at a higher frequency in younger subjects (<65 yrs and <75 yrs vs. >65 and >75 yrs, 32.4% and 25.7% vs. 14.7% and 6.8%, respectively).

Study US021-99 investigated the efficacy and safety of 4 mg daily (n=88) and 8 mg daily (n=90) of silodosin. As mentioned earlier, slightly more patients in the 8 mg silodosin arm experienced sexual dysfunction-type adverse events: retrograde ejaculation (15.6% vs. 11.4% in the 4 mg group and 0% in placebo arm) and ejaculation failure (11.1% vs. 9.1% patients in the 4 mg group, while it did not occur in the placebo group). Dizziness (8% vs. 5.6%), headache (5.7% vs. 2.2%) and positive orthostatic test (4.5% vs. 3.3%) occurred slightly more often in the 4 mg than in the 8 mg arm. The differences were not statistically significant.

In Japanese studies adverse drug reactions were observed in 391/873 (44.8%) patients treated with silodosin and in 28/178 (15.7%) patients treated with placebo.

Most common (1%) adverse reactions observed with silodosin in Japanese patients

Adverse Reaction	Silodosin (N=873)	Placebo (n=178)
Ejaculation disorder	11.7%	0.0%
Diarrhoea	7.7%	3.9%
Retrograde ejaculation	5.5%	0.0%
Thirst	5.5%	2.8%
Dizziness	5.0%	1.1%
Dizziness postural	3.6%	0.0%
Nasal congestion	3.3%	0.0%
Headache	2.7%	2.8%
Stomach discomfort	1.6%	1.1%
Constipation	1.4%	0.6%
Urinary incontinence	1.4%	0.0%
Malaise	1.4%	0.6%
Erectile dysfunction	1.3%	0.6%
Epistaxis	1.1%	0.6%

The information on adverse events is adequately reflected in the SmPC.

- Serious adverse event/deaths/other significant events

Three deaths occurred in the US clinical development programme of silodosin:
• acute myocardial infarction in a silodosin patient, considered not related by the investigator
• pulmonary embolism in a silodosin patient, considered not related by the investigator
• cerebral haemorrhage in a placebo patient.

In the European study IT-CL 0215 there were two deaths:
• severe lung squamous cell carcinoma (stage unspecified) in a silodosin patient, considered not related by the investigator;
• lung neoplasm malignant, renal cell carcinoma (stage unspecified), and adrenal carcinoma in a tamsulosin patient, considered not related by the investigator.

In placebo-controlled clinical trials serious adverse events (SAEs) occurred in 10/931 (1.1%) with silodosin and 8/733 (1.1%) with placebo. Overall, SAEs were reported by 47/1581 patients on silodosin. SAEs occurring in more than one patient were: myocardial infarction (5 cases), osteoarthritis (4 cases), lung neoplasm and prostate cancer (3 cases, each), gastric cancer, atrial fibrillation, pulmonary embolism, hip arthroplasty, urinary retention and diverticulitis (2 cases each).
One case of myocardial infarction was considered possibly related since there was no other evident pre-existing or concomitant condition that could explain the onset of the infarction. Nevertheless, this event occurred after 9 months of silodosin treatment, during which blood pressure, heart rate and ECGs had remained normal. One case of supraventricular arrhythmia was also reported in a 69-year-old patient with a relevant medical history of arterial hypertension. It was regarded as possibly related to the treatment.

One case of syncope occurred in a patient enrolled in the US study SI04010, also receiving a prohibited concomitant medication, the alpha-blocker prazosin. Since some cases of syncope have been reported in the postmarketing experience in Japan, syncope is considered as an identified risk and discussed in the Risk Management Plan. Moreover, the appropriate guidance on concomitant use of other alpha blockers has been included in the SmPC.

A formal ECG trial (study SI05014) demonstrated that silodosin at therapeutic (8 mg) and supra-therapeutic (24 mg) doses had no meaningful effects on heart rate, PR, and QRS interval duration. The effects on cardiac repolarisation, did not suggest that silodosin affected cardiac repolarisation. With regard to the EU/US phase II/III studies, no meaningful effect of silodosin on ECG categorisation was observed during the therapy for up to 1 year.

Three cases of prostatic cancer were reported. Since BPH and prostate carcinoma may present the same symptoms and can co-exist, patients suspected to have BPH should be examined prior to starting therapy with an alpha-blocker to rule out the presence of carcinoma of the prostate. The misdiagnosis of prostatic carcinoma during silodosin treatment is considered a potential risk and appropriate guidance has been included in the SmPC.

Other Significant Adverse Events

The "Intraoperative Floppy Iris Syndrome" (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery predominantly in some patients on or previously treated with tamsulosin. One case of IFIS occurred also with silodosin in the US open-label study SI04011 and in the post-marketing experience in Japan, while no cases were reported in the European study. Isolated reports have also been reported with other α-1 blockers, and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation, the ophthalmic surgeon should be informed before surgery on current or past use of α-1 blockers. IFIS is considered an identified risk and discussed in the Risk Management Plan. Appropriate guidance has been also included in the SmPC.

- Laboratory findings

Hypercreatininaemia was reported by 3 patients, however overall there is no evidence indicating that silodosin treatment may deteriorate renal function.

In non-clinical studies silodosin induced stimulation of TSH secretion in the male rat and decreased circulating levels of thyroxine (T4). In clinical studies including 40 weeks open label phase, blood TSH increased was reported in 3 patients. There was no evidence that silodosin may affect thyroid function. Moreover, in female mice treated for 2 years with silodosin doses of 150 mg/kg/day or greater had statistically significant increases in the incidence of mammary gland adenoacanthoma and adenocarcinomas considered secondary to silodosin-induced hyperprolactinemia. In two US phase III clinical studies serum prolactin levels were unaffected after 12 weeks of treatment.

Post-marketing data in Japan indicated occurrence of impaired hepatic function and jaundice, since some cases suspected of being related to silodosin have been reported. In the EU/US studies the only serious case of hepatitis was considered as not related (food poisoning) and resolved. Overall, there is no evidence to indicate that silodosin treatment may cause impaired hepatic function or jaundice.

In addition to standard clinical chemistry parameters, the following laboratory parameters were analysed: PSA, HbA1C, TSH, total T3, free T4, and total T4. Although in the integrated safety population, increased PSA was reported as treatment-emergent adverse event in 23 patients (1.5%), no significant change in serum PSA could be expected on silodosin therapy.

- Safety in special populations

Age

The incidence of adverse events by age was reviewed and no clinically relevant difference was observed for patients of different ages. Overall, silodosin appears to be well tolerated in the elderly and the incidence of the most common adverse reaction (retrograde ejaculation) is lower than in younger patients. There is no evidence of an increased risk of orthostatic hypotension in patients over 65 years. For the subgroup over 75 years the incidence of orthostatic hypotension in the silodosin group was slightly higher than in younger patients, however there is no statistical evidence of an increased risk.

Race

The majority (94.6%) of patients enrolled in the EU/US phase II and III studies were Caucasians. No integrated analyses of treatment-related adverse events by race have been conducted as the low percentage of patients of the other races would not provide meaningful data. However, in individual studies performed in the US, safety data was analysed by race and no differences were observed.

Renal Insufficiency
A large number of patients (487/1,581) in the overall silodosin safety population had mild renal impairment (CrCl of 80-50 ml/min). A high number of patients with mild renal impairment were also included in the placebo-controlled studies (273 for silodosin and 204 for placebo). Mild renal impairment does not confer additional safety risks, such as increased dizziness and orthostatic hypotension, during silodosin therapy in comparison with patients with normal renal function. No warning or dose adjustment is therefore required in these patients. The experience in patients with moderate renal impairment (n=35) and even more in severe renal impairment (n=1) is too limited to draw firm conclusions. The incidence of dizziness (2/35, 5.7%) was apparently increased in patients with moderate renal impairment in comparison with normal patients (20/955, 2.1%) or with patients with mild renal impairment (10/487, 2.1%). Orthostatic hypotension occurred in 2/35 (5.7%) patients with moderate renal impairment as compared with 2/487 (0.4%) with mild renal impairment and 15/955 (1.6%) with normal renal function. A starting dose of 4 mg is recommended for patients with moderate renal impairment, while the use of the product is not recommended in severe renal impairment. This information is adequately reflected in the SmPC.

Hepatic Insufficiency
On the basis of the clinical pharmacology study investigating the effects of hepatic dysfunction (Study SI05010), no dose adjustment is required for patients with mild to moderate hepatic impairment. The effects of severe hepatic insufficiency were not evaluated. The use of silodosin in these patients is therefore presently not recommended. This information is adequately reflected in the SmPC.

- Safety related to drug-drug interactions and other interactions

Antihypertensive medication
A large number of patients received concomitant treatment with antihypertensive agents during the clinical development programme. In particular, 24% of the patients were administered drugs acting on the renin-angiotensin system, 13% beta-blocking agents, 8.7% calcium antagonists and 7.5% diuretics. Only individual patients were treated concomitantly with α-adrenoceptor antagonists in violation of the protocol (2 with doxazosin, 1 with prazosin, 1 with terazosin).
A comparison of the safety data from patients on concomitant antihypertensive therapy and those not receiving the antihypertensive treatment indicate no increase in risk of orthostatic hypotension in patients taking antihypertensive agents. Dizziness was slightly more frequent in patients taking antihypertensive medication, while there is no increase in the number of patients complaining of vertigo, fatigue or asthenia. Appropriate guidance regarding concomitant use of antihypertensives has been included in the SmPC. The concomitant use of an α-adrenoceptor antagonist is not recommended, since clinically relevant interactions might occur.

PD interactions with PDE5 inhibitors
Results from the pharmacodynamic interaction study with silodosin and sildenafil, tadalafil, or placebo (Study SI06002) suggest a minimal risk of orthostatic hypotension due to and interaction between PDE5 inhibitors and silodosin. Data from placebo-controlled clinical studies show that orthostatic hypotension occurs more frequently in patients on PDE5 inhibitors both in the silodosin group (3/58, 5.2%) and in the placebo group (2/56, 3.6%) in comparison with patients not on concomitant treatment (8/873, 0.9% with silodosin and 5/677, 0.7% with placebo). Overall, orthostatic hypotension was reported by 4/114 patients treated with silodosin and PDE-5 inhibitors (3.5%), as compared to 16/1467 (1.1%) not on concomitant medications. Patients taking silodosin concomitantly with PDE-5 inhibitors should be monitored for possible adverse reactions. This information is adequately reflected in the SmPC.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
No clinical investigations have been performed examining silodosin potential to affect response time or coordination. Based on the clinical study results, as well as experience with other selective agents from this pharmacologic class, the likelihood of a significant effect is considered low. However, patients should be instructed about the possible occurrence of symptoms related to postural

hypotension (such as dizziness) and should be cautioned about driving or operating machinery until they know how silodosin will affect them. This information is adequately reflected in the SmPC.

- Discontinuation due to adverse events

During the double-blind phase of the US and EU studies, treatment-related adverse events leading to study discontinuation occurred in 40/931 (4.3%) patients treated with silodosin, as compared to 14/733 (1.9%) patients on placebo. Taking into consideration also the data collected in the open label long-term extension phase of the studies, overall 148/1581 (9.4%) subjects discontinued the study due to AEs during silodosin therapy. The most frequent cause of study discontinuation was retrograde ejaculation (62/1581, 3.9%). Dizziness was a cause of discontinuation in 8/1581 patients (0.5%) and orthostatic hypotension in 3/1581 patients (0.2%).

- Post marketing experience

The international birth date of silodosin is January 23, 2006. Silodosin was first approved in Japan and has been launched there in May 2006. The recommended dose in Japan is 4 mg twice daily after breakfast and the evening meal that can be reduced to 2 mg twice daily according to the patient's conditions. Based on cumulative sales of silodosin (Urief) in Japan from launch (May 2006) until 30th January 2008, approximately 344,000 patients have been exposed to silodosin during this period. Up to January 30, 2008, a total of 2,672 adverse reactions have been reported in Japan, including 98 cases assessed as serious, 2,570 as non-serious and 4 as unknown.
The most frequently reported adverse reactions have been abnormal ejaculation, diarrhoea, dizziness, nasal congestion and thirst. The large majority of those events were assessed as non serious.
The Company Safety Information was updated with the undesirable effects syncope, unconsciousness, and warnings/precautions including a class statement on IFIS, jaundice and hepatic function disorder.
In the drug usage survey presently ongoing in Japan no special safety issues have been identified.

- Discussion on clinical safety

A total of 3049 subjects received at least one dose of silodosin. A total of 1581 patients were exposed to the daily doses of 8 mg silodosin and were included in the integrated summary of safety; 961 (62.4%) patients were exposed for at least 6 months and 384 patients (24.9%) were exposed for at least 12 months. In addition, studies in Japan provided safety information on 873 patients and clinical pharmacology studies on 595 subjects.

In the integrated summary of safety the most common adverse events on silodosin treatment was an event coded as 'retrograde ejaculation' (23.6%). In the active-controlled study IT-CL-0215 retrograde ejaculation was reported by a significantly higher percentage of subjects in the silodosin treatment group (14.2%) compared with the tamsulosin treatment group (2.1%) and the placebo group (1.1%). It was the most common reason for withdrawal in this study and in the overall safety population of patients treated with silodosin (62/1581, 3.9%). The CHMP has expressed concern about the high rate of ejaculatory disorders in patients treated with silodosin and asked the applicant to discuss further this issue and other related adverse events as well as their impact on patients' sexual life. In their responses the applicant emphasised that retrograde ejaculation (i.e. orgasm with reduced or no semen) is due to the potent and selective alpha1A-adrenoreceptor antagonism of the drug, with consequent marked smooth muscle relaxation in the lower urinary and genital tract. There was no evidence for damage to the urological system and the effect of silodosin on ejaculation was transitory and reversible without permanent effects on fertility. Retrograde ejaculation was not perceived as bothersome by the majority of patients. In the clinical study programme conducted with silodosin this event lead to treatment discontinuation in a minority of patients (1.3% on silodosin arm compared to 0.3% on tamsulosin arm). Relevant warnings have been included in product labelling. To further investigate the psycho-sexological impact of the ejaculatory disturbances, a detailed PSUR review of adverse events regarding sexual life will be performed as a follow-up measure (FUM).

Other adverse reactions occurring in ≥1% of patients were dizziness (2.1%), nasal congestion (1.3%), headache (1.3%) and diarrhoea (1.0%). Orthostatic hypotension was reported by 20/1581 patients (1.3%), with an incidence similar to that observed with placebo (1.2% vs. 1.0%) in placebo-controlled studies. Comparative data with tamsulosin revealed that headache was reported by a somewhat lower

percentage of subjects in the silodosin group (2.9%) compared with the tamsulosin group (5.5%) and the placebo group (4.7%). The occurrence of related TEAE was not associated with onset or duration of treatment. Five deaths occurred during the clinical development programme. They were considered as not related by the investigators. In placebo-controlled clinical trials SAEs occurred in 10/931 (1.1%) with silodosin and 8/733 (1.1%) with placebo. The "Intraoperative Floppy Iris Syndrome" (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery predominantly in some patients on or previously treated with alpha-blocking agents. IFIS is considered an identified risk and discussed in the Risk Management Plan. Appropriate guidance has been also included in the SmPC. Moreover, a detailed PSUR review of cases of IFIS, orthostatic hypotension, syncope and photosensitivity reactions will be performed as a FUM.

Silodosin did not appear to prolong the QT interval.

Silodosin did not appear to have clinically meaningful effect on laboratory values tested, including serum PSA.

The frequency and profile of adverse events was similar in patients with normal renal function and mild renal impairment and in patients with < 65 and > 65 years of age. Concomitant disease such as hypertension did not have significant effect on the safety profile. There is a limited experience of silodosin use in patients with moderate renal failure and no experience in patients with severe renal failure and hepatic failure. This is adequately reflected in the SmPC. Moreover, a detailed PSUR review of the use of the 4 mg dose in moderate/severe renal impairment will be performed as a FUM.

Post-marketing experience with silodosin 4 mg bid from Japan has not identified any additional risks.

In conclusion, safety profile of silodosin can be considered similar to other alpha1-adrenoreceptor antagonists, except fort the higher frequency of retrograde ejaculation.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activity (routine/additional)**	**Proposed risk minimisation activities (routine/additional)**
Important identified risks		
IFIS	Routine pharmacovigilance Additional: - Expedited reporting of all extra-EU serious cases to EudraVigilance - Close monitoring and review of cases in the PSUR	Routine: Labelling: SmPC section 4.4 IFIS (a variant of small pupil syndrome) has been observed during cataract surgery in some patients on α_1-blockers or previously treated with α_1-blockers. This may lead to increased procedural complications during the operation. The initiation of therapy with Urorec is not recommended in patients for whom cataract surgery is scheduled. Discontinuing treatment with an α_1-blocker 1-2 weeks prior to cataract surgery has been recommended, but 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 Urorec, in order to ensure that appropriate measures will be in place to manage IFIS during surgery. SmPC section 4.8. Additional - Educational material to eye surgeons
Orthostatic hypotension	Routine pharmacovigilance Additional: - Expedited reporting of all extra-EU serious cases to EudraVigilance - Close monitoring and review of cases in the PSUR	Labelling: SmPC section 4.4 <u>Orthostatic effects</u> The incidence of orthostatic effects with Urorec is very low. However, a reduction in blood pressure can occur in individual patients, leading in rare cases to syncope. At the first signs of orthostatic hypotension (such as postural dizziness), the patient should sit or lie down until the symptoms have disappeared. In patients with orthostatic hypotension, treatment with Urorec is not recommended. SmPC section 4.7. SmPC section 4.8.

Safety concern	Proposed pharmacovigilance activity (routine/additional)	Proposed risk minimisation activities (routine/additional)
Syncope	Routine pharmacovigilance Additional: - Expedited reporting of all extra-EU serious cases to EudraVigilance - Close monitoring and review of cases in the PSUR	Labelling: SmPC section 4.4 <u>Orthostatic effects</u> The incidence of orthostatic effects with Urorec is very low. However, a reduction in blood pressure can occur in individual patients, leading in rare cases to syncope. At the first signs of orthostatic hypotension (such as postural dizziness), the patient should sit or lie down until the symptoms have disappeared. In patients with orthostatic hypotension, treatment with Urorec is not recommended. SmPC section 4.8.
Important potential risks		
Use in moderate/severe renal impairment	Routine pharmacovigilance Additional: - close monitoring and review of the 4 mg use in Europe in PSUR)	- Labelling SmPC section 4.2: Renal impairment 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 (see sections 4.4 and 5.2). SmPC section 4.4: Renal impairment The use of Urorec in patients with severe renal impairment (CLCR <30 ml/min) is not recommended (see sections 4.2 and 5.2). SmPC section 5.2.
Misdiagnosis of prostatic cancer	Routine pharmacovigilance	- Labelling SmPC section 4.4: Carcinoma of the prostate Since BPH and prostate carcinoma may present the same symptoms and can co-exist, patients thought to have BPH should be examined prior to starting therapy with Urorec, to rule out the presence of carcinoma of the prostate. Digital rectal examination and, when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.

Safety concern	Proposed pharmacovigilance activity (routine/additional)	Proposed risk minimisation activities (routine/additional)
Photosensitivity reactions	Routine pharmacovigilance Additional: - close monitoring and review in PSUR	- Labelling not required.
Abnormal ejaculation (retrograde ejaculation, anejaculation)	Routine pharmacovigilance Additional: - close monitoring and review of cases in the PSURs	- Labelling SmPC section 4.4: Treatment with Urorec leads to a decrease in the amount of semen released during orgasm that may temporarily affect male fertility. This effect disappears after discontinuation of Urorec (see section 4.8). SmPC section 4.6: <u>Fertility</u> In clinical studies, the occurrence of ejaculation with reduced or no semen has been observed during treatment with Urorec (see section 4.8), due to the pharmacodynamic properties of silodosin. Before starting treatment, the patient should be informed that this effect may occur, temporarily affecting male fertility. SmPC section 4.8.
Concomitant treatment with strong CYP 3A4 inhibitors	Routine pharmacovigilance	- Labelling SmPC section 4.5.
Concomitant use with other alpha-blockers.	Routine pharmacovigilance	- Labelling SmPC section 4.5.
Concomitant treatment with Phosphodiesterase type 5 inhibitors	Routine pharmacovigilance	- Labelling SmPC section 4.5.
Concomitant use with antihypertensives	Routine pharmacovigilance	- Labelling SmPC section 4.5

Safety concern	Proposed pharmacovigilance activity (routine/additional)	Proposed risk minimisation activities (routine/additional)
Missing information		
Use in severe hepatic impairment	Routine pharmacovigilance	- Labelling SmPC section 4.2: *Hepatic impairment* No dose adjustment is required for patients with mild to moderate hepatic impairment. As no data are available, the use in patients with severe hepatic impairment is not recommended (see sections 4.4 and 5.2). SmPC section 4.4: <u>Hepatic impairment</u> Since no data are available in patients with severe hepatic impairment, the use of Urorec in these patients is not recommended (see sections 4.2 and 5.2). SmPC section 5.2.
Concomitant use of 5-α-reductase inhibitors	Routine pharmacovigilance	- Labelling not required.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- Educational material to eye surgeons including the following:

- the Direct Healthcare Professional Communication (DHPC) on the association of Silodosin with Intraoperative Floppy Iris Syndrome and the two literature references mentioned in the text of the communication (at launch);

- a flow-chart describing the management of patients for which cataract surgery is scheduled (at launch and after launch);

- an educational programme on the prevention and management of IFIS (at launch and after launch); covering the following topics:

    1. clinically relevant literature references on the prevention and management of IFIS;

    2. pre-operative assessment: eye surgeons and ophthalmic teams should establish whether patients scheduled for cataract surgery are being or have been treated with silodosin in order to ensure that appropriate measures are in place to manage IFIS during surgery.

    3. recommendation to surgeons and ophthalmic teams: discontinuing treatment with α1-adrenoceptor antagonists 2 weeks prior to cataract surgery has been recommended, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
There are no unresolved quality issues which may affect the Benefit/Risk balance.

Non-clinical pharmacology and toxicology
The toxicological profile of silodosin was assessed in a sufficient set of studies which appropriately described the main characteristics of the product relevant for the proposed conditions of use. The main findings observed in the repeat-dose toxicology studies were related to enzymatic induction in the dog liver (fatty degeneration), increased prolactin production (changes in mammary gland and sex organs in female rats), stress (atrophy of the thymus and lipid accumulation), were considered to be a high dose phenomenon (atrophy of the fundic gland and oedema of stomach submucosa in rats and dogs) or irrelevant in terms of human safety (degeneration of the seminiferous tubular epithelium and delayed maturation of male genital organs in dogs). Following the detailed discussion on silodosin cardiac safety the CHMP has acknowledged that the product has little effect on the repolarisation process of the heart and is unlikely to cause a significant decrease in blood pressure. Similarly, the deposition of lipofuscin-like materials observed in dog hepatocytes was deemed not to be relevant to man due to minimal severity and absence of other histopathological findings and blood biochemical changes suggestive of hepatotoxicity. Silodosin was considered not to be genotoxic in a standard battery of tests. Neoplastic lesions observed in female mice, including mammary adenocarcinomas, adenoacanthoma, pituitary adenomas appeared to be related to the increased prolactin production as discussed in detail in responses to the CHMP questions. In male rats, an increase in incidence of thyroid follicular cell tumours was noted. The discussion provided by the applicant following the CHMP request indicated that these tumours were related to increased UDP-GT levels and disturbances of the T3 and T4 metabolism specific to rodents. There was no evidence of teratogenicity in rats or rabbits. Slight, but reversible, decreases in sperm counts and mobility were noted in male rats. In female rats, silodosin was associated with alterations in the oestrus cycle at high doses, but not with

infertility, although decreased fertility and implantation rates were also reported. *In vitro* and *in vivo* phototoxicity studies suggest that silodosin may have the ability to minimally increase sensitivity to sunlight.

All toxicology findings have been adequately reflected in the SmPC and risk management programme for silodosin.

Efficacy

The efficacy of silodosin was assessed in three main multicentre efficacy studies of 12-week duration conducted according to the classical randomised, double-blinded, controlled design. Two studies, SI04009 and SI04010, were conducted in the US and one (IT-CL-0215) in Europe. The European study was an active- and placebo-controlled trial. In all main studies 4-week single-blind placebo run-in period preceded 12 weeks of therapy with silodosin, placebo or active control (study IT-CL-0215). In the main studies 837 patients received silodosin, 376 active control (tamsulosin) and 642 placebo. The average age of patients enrolled in the studies was 65 years. In all studies the final marketing formulation of the product was used.

The primary endpoint used across the studies was a change from baseline in the total score of IPSS (International Prostate Symptom Score, Questions 1-7 referring to symptoms) as measured at week 12. A number of secondary endpoints were used including change in the maximum urine flow rate (Qmax), irritative and obstructive symptoms subscales of the IPSS and QOL. The safety of silodosin compared to placebo based on adverse events, vital signs (including orthostatic test), ECGs, clinical laboratory tests, and physical exams was also assessed. Additional secondary endpoints in the IT-CL 0215 study included percentage of respondents to IPSS, defined as percentage of patients with ≥ 25% decrease in IPSS compared to baseline, and percentage of respondents to Qmax, defined as percentage of patients with ≥ 30% increase in Qmax compared to baseline. The CHMP has considered the primary and secondary endpoints as appropriate given that the assessment of symptom severity is the most important outcome measure from the patient's perspective.

The treatment with silodosin was shown to be superior to placebo with respect to the change from baseline to week 12 in the total IPSS score in all main studies and non-inferior to treatment with tamsulosin in the European study.

The CHMP has discussed the following efficacy aspects of the main studies:

a) Exclusion from randomisation of patients eligible at screening but demonstrating a significant placebo response after a 4-week placebo run-in and its impact on the treatment effect.

The post-hoc analysis including also placebo responders defined as subjects showing a decrease in the total IPSS score >25% in the run-in period did not change the original conclusions of silodosin superiority versus placebo and non inferiority versus tamsulosin. Additional 231 subjects in the US studies (125 and 106 in SI04009 and SI04010, respectively) and 31 in the European study were included in the post-hoc analysis. The reasons for not including the remaining subjects were discussed sufficiently and acknowledged by the CHMP. Moreover, a post-hoc subgroup analysis conducted separately in patients with moderate or severe symptoms (IPSS total score < 20 or ≥ 20, respectively) in order to evaluate the efficacy of silodosin with respect to the severity of the condition and justify the cut-off of ≥13 in the IPSS score as an inclusion criterion was also performed. The results confirmed that the treatment effect observed both in patients with moderate and severe condition was in the same order of magnitude in as in the whole patient population.

b) Choice of the clinically important difference (-2 points) and the non-inferiority margin (-1.5 points) and the clinical relevance of the treatment effect (-2.3 to -2.8 points change in the IPSS score on the silodosin arm) for study IT-CL-0215.

The literature data review submitted in response to the CHMP question demonstrated that the change in the IPPS score from baseline observed in silodosin arms was similar to those reported for other alpha-blockers providing justification for the non-inferiority margin. Similarly, the value of -2 points in the IPSS total score was considered as clinically relevant based upon previous clinical evidence showing that the minimum level of perception of improvement among men with moderate symptoms was set at -1.9 points. In addition, recently published meta-analysis on alpha-blockers also showed that

the difference from placebo in American Urological Association Symptom Index/International Prostate Symptom Score was -1.92 points (superiority margin). Hence, it can be concluded that the treatment effect observed in the European study was similar to that observed in other trials with alpha-blocking agents.

c) Duration of the main efficacy studies of 12 weeks.
The CHMP acknowledged that in previous clinical studies with drugs approved for BPH, the duration of main efficacy studies has been 12 weeks due to the fact that alpha-blocking agents show immediate therapeutic benefits. Moreover, no regulatory guideline exists on the investigation of products for the treatment of BPH. The long-term benefits of silodosin have been shown in two open-label long-term studies in more than 900 patients treated for at least 6 months, and in more than 300 patients treated for 12 months. In both studies the treatment effect appeared soon after treatment initiation and was maintained over time. In acknowledging the response, the CHMP underlined the limited validity related to an uncontrolled design of the open-label extension trials.

Safety
A total of 3049 subjects received at least one dose of silodosin. A total of 1581 patients were exposed to the daily doses of 8 mg silodosin and were included in the integrated summary of safety; 961 (62.4%) patients were exposed for at least 6 months and 384 patients (24.9%) were exposed for at least 12 months. In addition, studies in Japan provided safety information on 873 patients and clinical pharmacology studies on 595 subjects. Size of the safety population, both in terms of number of patients and duration of treatment, meets requirements in the ICH Topic E1 "Population Exposure: The Extent of Population Exposure to Assess Clinical Safety". Demographic characteristics of the integrated safety population are representative of the target patient population.

In the integrated summary of safety the most common adverse event on silodosin treatment was an event coded as 'retrograde ejaculation' (23.6%). In the active-controlled study IT-CL-0215 retrograde ejaculation was reported by a significantly higher percentage of subjects in the silodosin treatment group (14.2%) compared with the tamsulosin treatment group (2.1%) and the placebo group (1.1%). It was also the most common reason for withdrawal in this study and in the overall safety population (3.9%). The CHMP has expressed concern about the high rate of ejaculatory disorders in patients treated with silodosin and asked the applicant to discuss further this issue and other related adverse events as well as their impact on patients' sexual life. In their responses the applicant emphasised that retrograde ejaculation (i.e. orgasm with reduced or no semen) is due to the potent and selective alpha 1A-adrenoreceptor antagonism of the drug, with consequent marked smooth muscle relaxation in the lower urinary and genital tract. There was no evidence for damage to the urological system and the effect of silodosin on ejaculation was transitory and reversible without permanent effects on fertility. Retrograde ejaculation was not perceived as bothersome by the majority of patients. In the clinical study programme conducted with silodosin this event lead to treatment discontinuation in a minority of patients (1.3% on silodosin arm compared to 0.3% on tamsulosin arm). Relevant warnings have been included in the product labelling.
To further investigate the psycho-sexological impact of the ejaculatory disturbances a close monitoring and review in PSURs of adverse events regarding sexual life is foreseen as a follow-up measure.

Other adverse reactions occurring in ≥1% of patients were dizziness, nasal congestion, headache and diarrhoea. Orthostatic hypotension was reported by 1.3% of patients with an incidence similar to that observed with placebo (1.2% vs. 1.0%) in placebo-controlled studies. The occurrence of related TEAE was not associated with onset or duration of treatment. Five deaths occurred during the clinical development programme. They were considered as not related by the investigators. In placebo-controlled clinical trials SAEs occurred in 1.1% with silodosin 1.1% with placebo. The "Intraoperative Floppy Iris Syndrome" (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery predominantly in some patients on or previously treated with alpha-blocking agents. IFIS is considered an identified risk and discussed in the Risk Management Plan. Appropriate guidance has been also included in the SmPC.

Silodosin did not appear to prolong the QT interval. Silodosin did not appear to have clinically meaningful effect on laboratory values tested, including serum PSA. The frequency and profile of adverse events was similar in patients with normal renal function and mild renal impairment and in patients with < 65 and > 65 years of age. Concomitant disease such as hypertension did not have significant effect on the safety profile. There is a limited experience of silodosin use in patients with moderate renal failure and no experience in patients with severe renal failure and hepatic failure. This is adequately reflected in the SmPC.

Post-marketing experience with silodosin 4 mg bid from Japan has not identified any additional risks.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 2.5 adequately addressed these.

- User consultation

The applicant has submitted results from the user testing of package leaflet which was performed in English. The results of the test were found to be acceptable.

Risk-benefit assessment
The treatment with silodosin was shown to be superior to placebo with respect to the change from baseline to week 12 in the total IPSS score (the overall treatment effect -2.3 to -2.8) in all main studies and non-inferior to treatment with tamsulosin in the European study. Additional analyses including also placebo responders did not change the original conclusions and confirmed that the treatment effect was significant both in patients with moderate and severe condition with slightly more pronounced effect in severe patients.
Clinical relevance of the observed absolute change in the IPSS score is difficult to establish. The IPSS score was used for the primary efficacy assessment. Although it is the most widely used questionnaire in clinical trials for BPH, it is not specific to BPH, but rather measures LUTS. The score has not been fully validated to meet regulatory requirements.
Interpretation of study results is further hampered by the use of enriched population.
The clinical development programme of silodosin has been similar to that of other alpha-blockers approved for the treatment of BPH. The literature review of studies conducted with alpha-blockers for the treatment of BPH has shown similar changes in the IPSS score as those observed with silodosin. Given that the results obtained for silodosin were very similar to those reported previously for other alpha-blockers and were confirmed in the tamsulosin-controlled EU study IT-CL0215, it can be concluded that the efficacy of silodosin has been demonstrated.

The safety profile of silodosin is comparable to that of other products in this therapeutic class (alpha 1-adrenoreceptor antagonists), except for the frequency of ejaculatory disorders. In a 12-week comparative trial, 14% of patients on silodosin arm compared to 2% of patients on tamsulosin arm reported retrograde ejaculation. However, retrograde ejaculation was not perceived as bothersome by the majority of patients. There is no evidence for damage to the urological system; the effect of silodosin on ejaculation is transitory and reversible without permanent effects on fertility. Other aspects of silodosin safety profile seem to be similar to those reported for other alpha 1-adrenoreceptor antagonists.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- the following additional risk minimisation activities were required: Direct Healthcare Professional Communication (DHPC) on the association of silodosin with Intraoperative Floppy Iris Syndrome (IFIS), a flow-chart describing the management of patients scheduled for cataract surgery, an educational programme on the prevention and management of IFIS.

A class waiver for paediatric studies have been issued by the EMEA.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Urorec in the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) was favourable and therefore recommended the granting of the marketing authorisation.