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Public Assessment Report

Name of the Product:

Silodosin Mylan
4 mg, 8 mg hard capsules

(silodosin)

Procedure number: HU/H/0606/001-002/DC

Marketing authorisation holder: Mylan Ireland Ltd.

Date: 4 Mach 2020

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Silodosin 4 mg, 8 mg hard capsules. The holder of the marketing authorisation is Mylan Ireland Ltd.

The active substance is silodosin. Each capsule contains 4 mg or 8 mg of silodosin.

The other ingredients are:
- capsule content: mannitol (E421), pregelatinised starch (maize), sodium laurilsulfate, glycerol dibehenate (E471);
- capsule shell:
  - 4 mg strength: gelatine, titanium dioxide (E171), yellow iron oxide (E172),
  - 8 mg strength: gelatine, titanium dioxide (E171);
- printing ink, black: shellac (E904), propylene glycol (E1520), ammonia solution, concentrated (E527), black iron oxide (E172), potassium hydroxide (E525).

The 4 mg hard capsules are yellow, opaque, hard gelatine capsules, size 3, printed with black ink "4" on the cap.

The 8 mg hard capsules are white, opaque, hard gelatine capsule, size 0, printed with black ink "8" on the cap.

Silodosin Mylan hard capsule belongs to a group of medicines called alpha$_{1A}$-adrenoreceptor blockers. It is selective for the receptors located in the prostate, bladder and urethra. By blocking these receptors, it causes smooth muscle in these tissues to relax. This makes it easier to pass water and relieves your symptoms.

Silodosin Mylan hard capsules (further on: Silodosin Mylan) is used in adult men to treat the urinary symptoms associated with benign enlargement of the prostate (prostatic hyperplasia), such as:
- difficulty in starting to pass water,
- a feeling of not completely emptying the bladder,
- a more frequent need to pass water, even at night.

What patients need to know before taking Silodosin Mylan

Patients, who are allergic to silodosin or any of the other ingredients of this medicine should not take Silodosin Mylan.

Warnings and precautions

Patients should talk to their doctor before taking Silodosin Mylan if they

- are undergoing eye surgery because of cloudiness of the lens (cataract surgery). It is important to inform the eye specialist immediately that Silodosin Mylan is being used or having been previously used. This is because some patients treated with this kind of medicine experienced a loss of muscle tone in the iris (the coloured circular part of the eye) during such a surgery. The specialist can take appropriate precautions with respect to medicine and surgical techniques to be used. Patients should ask their doctor whether or not they should postpone or temporarily stop taking Silodosin Mylan when undergoing cataract surgery;
- have ever fainted or felt dizzy when suddenly standing up. Dizziness when standing up and occasionally fainting may occur when taking Silodosin Mylan, particularly when starting treatment or if the patient is taking other medicines that lower blood pressure. If this occurs, the patient should make sure he/she sit or lie down straight away until the symptoms have disappeared and inform the doctor as soon as possible (see also section "Driving and using machines");
- have severe liver problems, for Silodosin Mylan should not be taken, as it was not tested in this condition;
- have problems with the kidneys, the doctor should be consulted for advice;
- have moderate kidney problems. The doctor will start Silodosin Mylan with caution and possibly with a lower dose;
- have severe kidney problems. Such patients should not take Silodosin Mylan.

Since a benign enlargement of the prostate and prostate cancer may present the same symptoms, the doctor will check the patient for prostate cancer before starting treatment with Silodosin Mylan. Silodosin Mylan does not treat prostate cancer.

The treatment with Silodosin Mylan may lead to an abnormal ejaculation (decrease in the amount of semen released during sex) that may temporarily affect male fertility. This effect disappears after discontinuation of Silodosin Mylan. Patients should inform their doctor if they are planning to have children.

Children and adolescents

This medicine should not be given to children and adolescents below 18 years since there is no relevant indication for this age group.

Other medicines and Silodosin Mylan

Patients should inform their doctor if they are taking, have recently taken or might take any other medicines.

In particular, if taking:
- Silodosin Mylan medicines which lower blood pressure (in particular, medicines called alpha$_1$-blockers, such as prazosin or doxazosin) as there may be the potential risk that the effect of these medicines is increased whilst taking Silodosin Mylan;
- antifungal medicines (such as ketoconazole or itraconazole), medicines used for HIV-AIDS (such as ritonavir) or medicines used after transplants to prevent organ rejection (such as

cyclosporin) because these medicines can increase the blood concentration of Silodosin Mylan;
- medicines used for treating problems in getting or keeping an erection (such as sildenafil or tadalafil), since the concomitant use with Silodosin Mylan might lead to a slight decrease in blood pressure;
- medicines for epilepsy or rifampicin (a medicine to treat tubercolosis), since the effect of Silodosin Mylan may be reduced.

Pregnancy and fertility

Pregnancy: since Silodosin Mylan is used to treat men with benign enlargement of the prostate, it is not for use in women.

Fertility: Silodosin Mylan may reduce the amount of sperm, leading temporarily to a reduced ability to father a child.

Driving and using machines

Patients should not drive or operate machines if they feel faint, dizzy, drowsy or have blurred vision.

Silodosin Mylan contains sodium.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

How to take Silodosin Mylan

The recommended dose is one capsule of Silodosin Mylan 8 mg per day by oral administration.

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

Patients with kidney problems

For patients who have moderate kidney problems the doctor may prescribe a different dose. For this purpose Silodosin Mylan 4 mg hard capsules are available.

What to do if more Silodosin Mylan has been taken than it should have been?

Patients, who have taken more than one capsule, inform their doctor as soon as possible. Those who become dizzy or feel weak, tell it their doctor straight away.

What to do if taking Silodosin Mylan has been forgotten?

Patients may take their capsule later the same day if they have forgotten to take it earlier. If it is almost time for the next dose, the missed dose should be skipped. Patients should not take a double dose to make up for a forgotten capsule.

May taking Silodosin Mylan be sopped?

If a patient stops the treatment, the symptoms may re-appear.

Possible side effects

Like all medicines, Silodosin Mylan can cause side effects, although not everybody experiences them.

Patients noticing any of the following allergic reactions: swelling of the face or throat, difficulty in breathing, feeling faint, itchy skin or hives should contact their doctor immediately since the consequences could become serious.

The most common side effect is a decrease in the amount of semen released during sex. This effect disappears after discontinuation of Silodosin Mylan. Patients who are planning to have children should inform their doctor.

Dizziness, including dizziness when standing up, and occasionally fainting, may occur. If a patient do feel weak or dizzy, he/she should be sure to sit or lie down straight away until the symptoms have disappeared. If dizziness when standing up or fainting occurs, the doctor should be informed as soon as possible.

Silodosin Mylan may cause complications during a cataract surgery (eye surgery because of cloudiness of the lens, see section "Warnings and precautions"). It is important to inform the eye specialist immediately if the patient is using or has previously used Silodosin Mylan.

The possible side effects are listed below:

Very common side effects (may affect more than 1 in 10 people): abnormal ejaculation (less or no noticeable semen is released during sex, see section "Warnings and precautions")

Common side effects (may affect up to 1 in 10 people):
- dizziness, including dizziness when standing up (see also above, in this section),
- runny or blocked nose,
- diarrhoea.

Uncommon side effects (may affect up to 1 in 100 people):
- decreased sexual drive,
- nausea,
- dry mouth,
- difficulties in getting or keeping an erection,

- faster heart rate,
- symptoms of allergic reaction affecting the skin like rash, itching, hives and rash caused by the medicine,
- abnormal results of liver function tests,
- low blood pressure.

Rare side effects (may affect up to 1 in 1,000 people):
- fast or irregular heartbeats (called palpitations),
- fainting/loss of consciousness.

Very rare side effects (may affect up to 1 in 10,000 people): other allergic reactions with swelling of the face or throat

Side effect, which frequency cannot be estimated from the available data: floppy pupil during cataract surgery (see also above, in this section).

If patients feel that their sexual life is affected, tell it their doctor.

How to store Silodosin Mylan

It should be stored in the original package in order to protect from light and kept out of the sight and reach of children.

7

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Silodosin Mylan 4 mg, 8 mg hard capsules. The procedure was finalised at 11 February 2019. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Spain, France, Italy, Portugal and the Slovak Republic) concerned the generic version of silodosin 4 mg and 8 mg hard capsules (Silodosin Mylan capsules).

The application has been filed according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The originator product has been Urorec/Silodyx (4 and 8 mg, hard capsules) by Recordati Ireland Ltd., authorised for marketing since 2010 in the European Union.

To support the application, the applicant has submitted as report one pilot and one pivotal bioequivalence study in fed state. The reference product used in the bioequivalence studies was Silodyx 8 mg hard capsules (Recordati Ireland Ltd.). The applicant has adequately demonstrated bioequivalence between the product and reference product.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Silodosin Mylan 4 mg, 8 mg hard capsules (Mylan Ireland Ltd.)

The products are indicated for treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Silodosin 4 mg and 8 mg hard capsules via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The reference product has been Silodyx® hard capsule containing silodosin as active ingredient, which is the original product of Recordati Ltd.

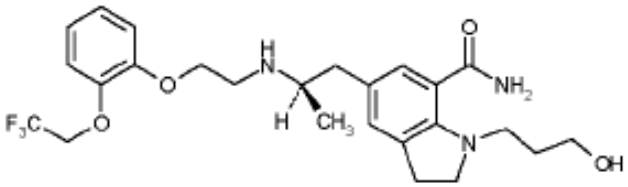
II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International Non-proprietary Name (INN): silodosin

Chemical name: 2,3-Dihydro-1-(3-hydroxypropyl)-5-[(2R)-2-[[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl]amino]propyl]-1H-indole-7-carboxamide
or
(-)-1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-rifluoro-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihyd-ro-1H-indole-7-carboxamide

Structure:



The active substance is white, almost white crystalline powder, freely soluble in chloroform, ethanol and methanol, soluble in acetone, sparingly soluble in acetonitrile and ethyl acetate, practically insoluble in heptane and water. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by IR, UV, 1H-NMR, 13C-NMR, DEPT (Distortionless Enhancement by Polarization Transfer) 135°, 1H-1H COSY (correlation spectroscopy), HMQC (Heteronuclear Multiple Quantum Correlation), HMBC (Heteronuclear Multiple Bond Correlation), mass spectrometry and elemental analysis. The impurity profile of

the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Silodosin is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the drug substance by the drug product manufacturer, according to the following requirements of the active substance manufacturer: description, identification (IR, HPLC), sulphated ash, water content, related substances (HPLC), assay (HPLC), isomer content, residual solvents, residual reagents. The specification of the drug product manufacturer is supplemented by additional specifications for polymorphic form, particle size and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council of Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch-to-batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented data the proposed re-test period is acceptable if stored in tight container in the original package.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop hard gelatine capsules containing silodosin as drug substance in 4 and 8 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal products Silodyx®, the branded original products of Recordati Ltd.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile, the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

The product 4 mg hard capsules are yellow, opaque, hard gelatine capsules, size 3, printed with black ink "4" on the cap. The 8 mg hard capsules are White, opaque, hard gelatine capsules, size 0, printed with black ink "8" on the cap.

The excipients used in the finished product are mannitol, pregelatinised starch, sodium laurilsulfate, and glycerol dibehenate, the capsule shells consist of gelatine, titanium dioxide as well as yellow iron oxide in the 4 mg strength. All excipients used comply with their respective Ph. Eur. monograph or the relevant EMA guidelines. Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is PVC/PE/PVDC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years if stored in the original package in order to protect from light is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view, the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of silodosin are well known. As silodosin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

The submitted non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology of silodosin is considered adequate.

III.2 Pharmacology

Silodosin is highly selective for α_{1A}-adrenoreceptors. Blockade of these a_{1A}-adrenoreceptors causes smooth muscle in these tissues to relax, thus decreasing bladder outlet resistance, without affecting detrusor smooth muscle contractility.

Silodosin has a substantially lower affinity for the α_{1B}-adrenoreceptors that are primarily located in the cardiovascular system. It has been demonstrated in vitro that the α_{1A}:α_{1B} binding ratio of silodosin (162:1) is extremely high.

III.3 Pharmacokinetics

Silodosin administered orally is well absorbed and absorption is dose proportional. An *in vitro* study with Caco-2 cells showed that silodosin is a substrate for P-glycoprotein. Food decreases C_{max}, increases t_{max} and has little effect on AUC.

Distribution: silodosin is mainly bound to plasma proteins. It does not distribute into blood cells.

Silodosin undergoes extensive metabolism through glucuronidation (UGT2B7), alcohol and aldehyde dehydrogenase and oxidative pathways, mainly CYP3A4. The main metabolite in plasma is the glucuronide conjugate of silodosin, that has been shown to be active *in vitro*. *In vitro* data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Silodosin is excreted mainly as metabolites, very low amounts of unchanged drug are recovered in urine.

III.4 Toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, carcinogenic, mutagenic and teratogenic potential. Effects in animals (affecting

the thyroid gland in rodents) were observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

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

III.5 Ecotoxicology/environmental risk assessment (ERA)

The product is intended as a substitute for the originator product on the market. The approval of this product will not result in an increase in the total quantity of silodosin released into the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of silodosin are well-known. No new non-clinical studies were conducted, which is acceptable for generic applications.

There are no objections to the approval of these applications from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

Silodosin is a recently developed, highly selective, once-daily dosing antagonist of α_{1A}-receptors. When these receptors are activated, they cause the muscles controlling the flow of urine to contract. By blocking these receptors, silodosin allows these muscles to relax, making it easier to pass urine and relieving the symptoms of BPH.

The clinical pharmacodynamics, pharmacokinetics, efficacy and safety of the active ingredient in the proposed indications, doses and dosing regimens are well known.

The application contains an adequate review of published clinical data.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC.

The proposed indication is: treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Silodosin administered orally is well absorbed and absorption is dose proportional. The bioavailability of silodosin is nearly 32%. Time to peak concentration of silodosin occurs at approximately 2.6 hours after drug intake. It has been shown that food is involved in the pharmacokinetic pathway of the drug. Thus, AUC and C_{max} decrease by 4% to 49% and by 18% to 43%, respectively, with a moderate calorie/fat meal. Moreover, food intake delays time to C_{max} by about one hour. Silodosin is recommended to be taken with food in order to avoid the potential side effects associated with high plasma drug concentrations.

Silodosin has a volume of distribution of 0.81 l/kg (49.5 L) after a single intravenous administration of a 2 mg of silodosin over a 4 h infusion (Study KMD-308) and is 96.6 % bound to plasma proteins. Silodosin did not distribute to blood cells in the study assessing plasma-blood partition (PK10091).

Silodosin is extensively hepatically metabolized through glucuronidation, alcohol and aldehyde dehydrogenase, and CYP3A4 pathways. Therefore, clinicians should not prescribe silodosin for patients who are also receiving CYP3A4 inhibitors such as ketoconazole and ritonavir, however, it can be prescribed for those taking moderate CYP3A4 inhibitors, such as diltiazem, or phosphodiesterase-5 inhibitors without significant

changes in blood pressure and heart rate. The main metabolite in plasma, the glucuronide conjugate of silodosin (KMD-3213G), this metabolite is generated via the glucuronidation pathway. It has been shown to be active *in vitro*, has an extended half-life (approximately 24 hours) and reaches plasma concentrations approximately four times higher than those of silodosin and an AUC three- or four fold higher than for the parent compound. Therefore, silodosin and its active metabolite have an extended half-life that makes once-daily dosing possible.

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

IV.2.2 Bioequivalence studies

To support the application, the applicant has submitted one pilot and one pivotal bioequivalence study in healthy adult man volunteers under fed conditions according to the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**). The pivotal bioequivalence study was conducted between Silodosin 8 mg hard capsule (Test) and Silodyx™ 8 mg hard capsule (manufactured by: Recordati Industria, Italy, for Recordati Ireland Ltd., Ireland, Reference).

The applicant has submitted biowaiver request for the 4 mg strengths, which was supported by dissolution data.

The objective of the pivotal study (based on the pilot one) was to evaluate and compare the bioavailability and therefore to assess the bioequivalence of two different formulations of silodosin after a single oral dose administration under fed conditions.

One bioequivalence study is considered sufficient with the highest strength (8 mg) for this product (see also assessment of biowaiver below). According to the *Guideline on the investigation of bioequivalence* (CPMP/QWP/EWP/1401/98 Rev. 1) the study in fed state is considered acceptable as the originator product should be taken with food.

Blood samples were taken prior to drug administration and at suitable time intervals following drug administration.

The analytical method has been sufficiently validated (pre-study and within study).
Results of ISR (incurred samples reanalysis) and analytical method validation fulfilled all the requested acceptance criteria according to the *Guideline on bioanalytical method validation* (EMEA/CHMP/EWP/192217/2009, 21 July 2011). Long-term storage stability has been adequately documented.

On the basis of results of pivotal bioequivalence study coded the single dose of the Test product and a single dose of Reference product are bioequivalent in healthy adult subjects under fed conditions.

Summary of bioequivalence evaluation:

Pharmacokinetic parameter	Ratio (Test/Reference)	90% Confidence interval	Intrasubject CV %
C_{max}	98.98	92.41 – 106.02	15.2
AUC_{0-t}	97.92	92.22 – 103.97	13.2

Biowaiver

Based on the linear pharmacokinetics of silodosin in the claimed dose strengths and on the results of dissolution tests with Silodosin 4 mg and Silodyx® 8 mg (reference product) the biowaiver request for Silodosin 4 mg hard capsule can be considered acceptable. All of the criteria (same manufacturer, manufacturing process, qualitative composition, quantitatively proportional composition of the different strengths) stated in the above bioequivalence guideline are justified.

Thus, the results of the pivotal study with 8 mg hard capsules formulation can be extrapolated to other 4 mg strength.

Conclusion on bioequivalence studies

Based on the results of the study report, bioequivalence between the Test and Reference product has been shown.

Safety issues: administration of the Test and Reference products to healthy subjects was safe and well tolerated. No new safety concern was identified.

IV.3 Pharmacodynamics

The drug product contains active substance silodosin. Silodosin is an alpha-adrenoreceptor antagonist. It is highly selective for α_1A-adrenoreceptors that are primarily located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these α_1A-adrenoreceptors causes smooth muscle in these tissues to relax, thus decreasing bladder outlet resistance, without affecting detrusor smooth muscle contractility. This causes an improvement of both storage (irritative) and voiding (obstructive) symptoms (Lower urinary tract symptoms, LUTS) associated with benign prostatic hyperplasia.

IV.4 Clinical efficacy

When compared to other currently available α_1-AR antagonists, silodosin is 1400 times more specific in terms of α_1A-AR versus α_1B-AR binding than doxazosin and terazosin and 40 times

greater compared to tamsulosin. The increased selectivity for α_1A-AR is postulated to provide additional relief of LUTS in patients with BPH without increasing the rate of serious adverse cardiovascular effects due to systemic α-AR antagonism.

No new efficacy data have been submitted and none are required for applications of this type.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	− Intraoperative Floppy Iris Syndrome (IFIS) − Orthostatic hypotension/hypotension − Syncope/loss of consciousness − Hypersensitivity (including allergic type reactions, such as facial edema, pharyngeal edema and swollen tongue) − Abnormal Liver Function Tests (LFTs) − Tachycardia − Palpitations − Abnormal ejaculation , erectile dysfunction
Important potential risks	− Use in moderate/severe renal impairment − Misdiagnosis of prostate cancer − Photosensitivity reactions − Genital discomfort/burning − Gynaecomastia, breast enlargement, breast tenderness − Use in patients with pre-existing cardiovascular disease − Concomitant treatment with strong CYP 3A4 inhibitors − Concomitant use with other alpha-blockers − Concomitant treatment with phosphodiesterase type 5 inhibitors

Summary of safety concerns	
	– Concomitant use with antihypertensive medicines
Missing information	– Use in severe hepatic impairment – Use in patients with a serum creatinine >2.0 mg/dL – Concomitant use of 5-alpha-reductase inhibitors – Patients aged ≥ 75 years

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Mylan's products containing silodosin. No additional activities are needed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Mylan's products containing silodosin. No additional activities are requested. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The application contains an adequate review of published clinical data and the bioequivalence between Silodosin 8 mg hard capsule and Silodyx 8 mg hard capsule has been shown. As the lower strengths meet the biowaiver criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1), the results and conclusions of the bioequivalence study can be extrapolated to the 4 mg strength.

Approval is recommended from the clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Silodosin Mylan 4 mg and 8 mg hard capsules, generic versions of silodosin. The future holder of authorisation is Mylan Ireland Ltd.

The products are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in adult men.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator and reference product was Silodyx (Urorec) 8 mg, hard capsules by Recordati Ireland Ltd., authorised for marketing since 2010 in the European Union.

To support the application the applicant has adequately justified the biowaiver for the 4 mg dose strength on the basis of bioequivalence guideline (*Appendix III, CPMP/EWP/QWP/1401/98/rev 1/Corr***).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Silodosin Mylan 4 mg and 8 mg hard capsules.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached