

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

PL 24668/0144-6

UKPAR

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SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

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LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets (PL 24668/0144-6) on 11 July 2012. These are prescription-only medicines (POM).

Sildenafil belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. Sildenafil will only help you get an erection if you are sexually stimulated. You should take sildenafil if you do not have erectile dysfunction. You should not take sildenafil if you are woman. Sildenafil is a treatment for men with erectile dysfunction, which is sometimes known as impotence. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

Based on the data submitted by Caduceus Pharma Limited, Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets were considered to be generic versions of the innovator products, Viagra 25 mg, 50 mg and 100 mg Film-Coated Tablets.

No new or unexpected safety concerns arose from these applications. It was judged that the benefits of Sildenafil 25 mg, 50 mg and 100 mg Film Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Sildenafil 25 mg , 50 mg and 100 mg Film Coated Tablets (PL 24668/0114017/0228-0231) to Caduceus Pharma Limited on 11th July 2012. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC as amended. The products are claimed to be generic medicinal products of the innovator products, Viagra 25 mg, 50 mg and 100 mg Film-Coated Tablets (EU/1/98/077/013, EU/1/98/077/002, EU/1/98/077/003), licensed to Pfizer Limited via the Centralised Procedure since September 1998. The innovator products have been authorised in the EEA for over 10 years.

Sildenafil 25 mg, 50 mg and 100 mg Film Coated Tablets contain the active ingredient sildenafil (as sildenafil citrate), which belongs to the pharmacotherapeutic group ‘drugs used in erectile dysfunction’ (ATC code-G04B E03). The tablets are indicated for the treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for sildenafil to be effective, sexual stimulation is required.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP; therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of the innovator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study comparing the test product Sildenafil 100 mg Film-Coated Tablets (Caduceus Pharma Limited) to the reference product Viagra 100 mg Film-Coated Tablets (Pfizer Limited) under fasting conditions, was submitted to support these applications. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations were granted.

PHARMACEUTICAL ASSESSMENT

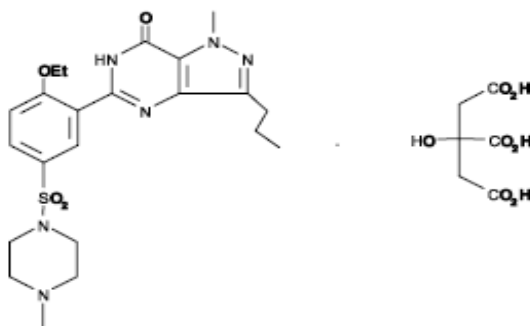
ACTIVE SUBSTANCE

Sildenafil Citrate

INN/ BAN: Sildenafil Citrate

Chemical name: 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1 H-pyrazolo [4,3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine, citrate (1:1).

Structure



Molecular formula: $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$

Molecular weight: 666.71

General Properties

Description: White to off-white powder

Solubility: Soluble in dimethylformamide, sparingly soluble in acetic acid and slightly soluble in methanol

The active substance, sildenafil citrate, is currently not the subject of a European Pharmacopoeia (Ph.Eur) or British Pharmacopoeia (BP) monograph.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active substance are not of animal, biological or genetically modified origin.

Appropriate data have been supplied to characterise the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the

relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and an appropriate retest period has been supplied.

MEDICINAL PRODUCT

Description and Composition

Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets are presented as blue elliptical, biconvex film-coated tablets marked with 'SL25'/'SL50'/'SL100' engraved on one side and plain on the other side. Each tablet contains 25 mg, 50 mg and 100 mg of the active ingredient, sildenafil (as sildenafil citrate).

Other ingredients consist of pharmaceutical excipients: lactose monohydrate, microcrystalline cellulose, povidone K29-32, croscarmellose sodium, magnesium stearate making up the tablet core and hypromellose, titanium dioxide (E171), macrogol 6000 and indigo carmine-aluminium lake (E132) constituting the film-coating. Appropriate justification for the inclusion of each excipient has been provided.

All excipients of the tablet cores and the film-coating comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. Magnesium stearate has been confirmed as being of vegetable origin. None of the excipients are sourced from genetically modified organisms. There are no novel excipients used.

Pharmaceutical Development

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The objective was to develop stable, generic, tablet formulations bioequivalent and pharmaceutically equivalent to the innovator's products, Viagra[®] 25 mg, 50 mg and 100mg film-coated tablets (Pfizer Limited).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles of the drug products were found to be similar to those of the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on commercial scale batches and results were acceptable.

Finished Product Specification

Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in polyvinylidene chloride (PVdC) coated polyvinylchloride (PVC) blister strips sealed with aluminium foil. The blister strips are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 2, 4, 8 and 12 tablets. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 3 years has been approved, with the following storage instructions, "Store below 30°C".

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Sildenafil 100 mg film-coated tablets, to the innovator's product; Viagra 100 mg film-coated tablets (Pfizer Ltd.,UK). The applicant has provided a suitable justification for a biowaiver for the other strengths (25 mg and 50 mg).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Quality Overall Summary

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the Competent Authority for approval before packs are marketed. The labelling texts fulfil the statutory requirements for Braille. The user-testing of the PIL text has been evaluated and is accepted.

Marketing Authorisation Application (MAA) Forms

The MAA forms are satisfactory.

Conclusion

There are no objections to approval of Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC, as amended, for Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets.

Specific non-clinical studies have not been performed, which is acceptable considering that these applications are for generic versions of products that have been licensed for over 10 years.

The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic and toxicological properties of sildenafil, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied.

No formal Environmental Risk Assessment has been provided. The applicant has justified the absence adequately. As the products have been used for over 10 years, the use of these products is not expected to increase the overall use of sildenafil and so no additional increase in environmental risk has been identified.

The SmPCs are satisfactory from a non-clinical viewpoint.

There are no objections to the approval of Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets from a non-clinical point of view.

CLINICAL ASSESSMENT

BACKGROUND

The active substance, sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP; therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

In October 2005, sildenafil was approved for the treatment of pulmonary arterial hypertension in a single dosage form (20 mg film-coated tablets), marketed under the name of Revatio by Pfizer Limited.

THERAPEUTIC INDICATIONS

Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets are indicated for the treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for Sildenafil to be effective, sexual stimulation is required.

The indications are consistent with those for the innovator products and are satisfactory.

POSODOLOGY AND METHOD OF ADMINISTRATION

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the innovator products and is satisfactory.

TOXICOLOGY

The toxicology of sildenafil is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of sildenafil is well-known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics-bioequivalence study

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product Sildenafil 100 mg Film Coated Tablets, to that of the reference product Viagra 100 mg Film-Coated Tablets (Pfizer Limited). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was a single dose randomised, two sequence, two-period crossover oral bioavailability study of conventional design in 32 healthy volunteers under fasting conditions. Following an overnight fast, a single dose of the investigational products was administered orally to each subject in each period. A washout period of at least 5 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 24 hours after administration of test or reference products. Plasma levels of sildenafil and its major metabolite N-desmethyl sildenafil were detected by a validated LC MS/MS analytical method.

The primary pharmacokinetic parameters for this study were C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-125 (80.00-125.00%), for log-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ for sildenafil and N-desmethyl sildenafil

Results

A summary of the results of the bioequivalence study is tabulated below:

Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of sildenafil

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)		A/B	Lower Limit
AUC _{0-t}	2209.776	2182.882	1.01	0.96	1.07
AUC _{0-inf}	2243.196	2217.495	1.01	0.96	1.06
C _{max}	658.462	581.706	1.13	1.02	1.25

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.

C _{max}	maximum plasma concentration
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity

Pharmacokinetic parameters (geometric means, ratios and confidence intervals [CI]) of N-Desmethyl sildenafil

Parameters	*Geometric mean		% Ratio	90 % Confidence Interval for Log-transformed data	
	Test (A)	Reference (B)	A/B	Lower Limit	Upper Limit
AUC _{0-t}	377.305	374.857	1.01	0.95	1.06
AUC _{0-inf}	396.559	395.095	1.00	0.95	1.06
C _{max}	78.696	71.230	1.10	1.00	1.22
*Geometric mean was taken as the antilog (exponential) of the Least square mean of the log-transformed data.					
C _{max}	maximum plasma concentration				
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours				
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity				

Conclusion on Bioequivalence

The results of the bioequivalence study show that the 100 mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and AUC_{0-∞} fall within the acceptance criteria ranges of 80-125% in line with CPMP/EWP/QWP/1401/98Rev1, NfG on the Investigation of Bioequivalence .

Satisfactory justification is provided for a bio-waiver for Sildenafil 25 mg and 50 mg Film-Coated Tablets. As Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets meet the 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 on the 100 mg strength can be extrapolated to the 25 mg and 50 mg strength tablets.

CLINICAL EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of sildenafil is well-established from its extensive used in clinical practice.

CLINICAL SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of sildenafil is well-known.

The MHRA considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected occurring either in the Community or in a third country.

The applicant did not submit a Risk Management Plan. This approach was justified on the basis of the similarity of the risks and benefits of the applicant’s products to those of the reference products, which at the time of the application did not have a Risk Management Plan in place. This justification has been accepted. If, in future, risk

minimisation measures are adopted for the reference products, the applicant will be obliged to implement similar measures for their products.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are fully harmonised with those for the reference products and are acceptable.

Patient Information Leaflet (PIL)

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Clinical Overview

A satisfactory clinical overview was provided and prepared by an appropriately qualified expert. The CV of the clinical expert was supplied.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Sildenafil 100 mg Film-Coated Tablets (Caduceus Pharma Limited) and the reference product, Viagra 100 mg Film Coated Tablets (Pfizer Limited).

As Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev.1/Corr), the results and conclusions of the bioequivalence study on the 100 mg strength were extrapolated to the 25 and 50 mg strength tablets and omission of further bioequivalence studies on the lower strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SmPCs are consistent with those of the innovator products and are satisfactory.

The PIL texts are in line with the SmPCs and are satisfactory. The leaflet text 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 results show that the leaflet text 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.

The approved labelling texts are satisfactory and fulfil the statutory requirements for Braille.

The MAH has submitted text versions only for the PIL and labelling and has committed to submitting mock-up livery to the competent authorities for approval before packs are marketed.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with sildenafil is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

PL 24668/0144-6

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 17 November 2010.
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 January 2012.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 6 June 2011 and the clinical dossiers on 31 May 2011
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 19 October 2011 and the clinical dossier on 22 July 2011.
5	The applications were determined on 12 July 2012

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

PL 24668/0144-6

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPCs) for Sildenafil 25 mg, 50 mg and 100 mg Film-Coated Tablets (PL 24668/0144-6) is as follows. Differences between the SmPCs are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Sildenafil 25 mg film-coated tablets
Sildenafil 50 mg film-coated tablets
Sildenafil 100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sildenafil 25 mg film-coated tablets

Each film-coated tablet contains 35.12 mg of sildenafil citrate corresponding to 25 mg of sildenafil base.

Excipient with known effect: 62.38 mg of lactose monohydrate per film-coated tablet.

Sildenafil 50 mg film-coated tablets

Each film-coated tablet contains 70.24 mg of sildenafil citrate corresponding to 50 mg of sildenafil base.

Excipient with known effect: 124.76 mg of lactose monohydrate per film-coated tablet.

Sildenafil 100 mg film-coated tablets

Each film-coated tablet contains 140.48 mg of sildenafil citrate corresponding to 100 mg of sildenafil base.

Excipient with known effect: 249.52 mg of lactose monohydrate per film-coated tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

blue, elliptical, biconvex marked 'SL25'/'SL50'/'SL100' respective of tablet strength on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Sildenafil to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Method of administration

For oral use

Posology

Use in adults:

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity.

Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg.

The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is

once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Use in the elderly:

Dosage adjustments are not required in elderly patients.

Use in patients with impaired renal function:

The dosing recommendations described in 'Use in adults' apply to patients with mild to moderate renal impairment (creatinine clearance = 30 - 80 ml/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30 ml/min) a 25 mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in patients with impaired hepatic function:

Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50mg and 100mg.

Paediatric population:

Sildenafil is not indicated for individuals below 18 years of age.

Use in patients using other medicines:

With the exception of ritonavir for which co-administration with sildenafil is not advised (see section 4.4) a starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors (see section 4.5).

In order to minimise the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered (see sections 4.4 and 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.

Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).

Sildenafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as *retinitis pigmentosa* (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4.4 Special warnings and precautions for use

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, especially in combination with sexual activity. Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.

Sildenafil potentiates the hypotensive effect of nitrates (see section 4.3).

Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of Sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of Sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.

Agents for the treatment of erectile dysfunction, including sildenafil, should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia).

The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking Sildenafil and consult a physician immediately (see section 4.3).

Co-administration of sildenafil with ritonavir is not advised (see section 4.5).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see section 4.5). This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered (see section 4.2). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.

Sildenafil tablets contain lactose and should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Sildenafil is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on sildenafil

In vitro studies:

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

In vivo studies:

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500mg twice daily) with sildenafil (100mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200ng/ml, compared to approximately 5ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised (see section 4.4) and in any event the maximum dose of sildenafil should under no circumstances exceed 25mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200mg three times a day) with sildenafil (100mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics (see section 4.2). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

When a single 100mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC, C_{max} , T_{max} , elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50mg) to healthy volunteers.

Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.

Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.

Effects of sildenafil on other medicinal products

***In vitro* studies:**

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ($IC_{50} > 150 \mu M$). Given sildenafil peak plasma concentrations of approximately $1 \mu M$ after recommended doses, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes.

There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.

***In vivo* studies:**

Consistent with its known effects on the nitric oxide/cGMP pathway (see section 5.1), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated (see section 4.3).

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing (see sections 4.2 and 4.4). In three specific drug-drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.

No significant interactions were shown when sildenafil (50mg) was co-administered with tolbutamide (250mg) or warfarin (40mg), both of which are metabolised by CYP2C9.

Sildenafil (50mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150mg).

Sildenafil (50mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.

Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-

adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers (see Section 5.1).

Sildenafil (100mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

4.6 Fertility, pregnancy and lactation

Sildenafil is not indicated for use by women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of Sildenafil is based on 8,691 patients who received the recommended dosing regimen in 67 placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, visual disorders, nasal congestion, dizziness and visual colour distortion.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

In the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $1/1,000$)).

In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies and medically important adverse reactions reported through postmarketing surveillance

System Organ Class	Adverse Reaction
--------------------	------------------

Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, Hypoaesthesia
Rare	Cerebrovascular accident, Syncope
Not known	Transient ischaemic attack, Seizure, Seizure recurrence
Eye disorders	
Common	Visual disorders, Visual colour distortion
Uncommon	Conjunctival disorders, Eye disorders, Lacrimation disorders, Other eye disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect.
Ear and labyrinth disorders	
Uncommon	Vertigo, Tinnitus
Rare	Deafness*
Vascular disorders	
Common	Flushing
Rare	Hypertension, Hypotension
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Myocardial infarction, Atrial fibrillation
Not known	Ventricular arrhythmia, Unstable angina, Sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, Nausea, Dry mouth
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash

Not known	Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Not known	Priapism, Prolonged erection
General disorders and administration site conditions	
Uncommon	Chest pain, Fatigue
Investigations	
Uncommon	Heart rate increased

*Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil.

4.9 Overdose

In single dose volunteer studies of doses up to 800mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in erectile dysfunction

ATC CODE: G04B E03

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. Nitric oxide then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

Studies *in vitro* have shown that sildenafil is selective for PDE5, which is involved in the erection process. Its effect is more potent on PDE5 than on other known phosphodiesterases. There is a 10-fold selectivity over PDE6 which is involved in the phototransduction pathway in the retina. At maximum recommended doses, there is an 80-fold selectivity over PDE1, and over 700-fold over PDE 2, 3, 4, 7, 8, 9, 10 and 11. In particular, sildenafil has greater than 4,000-fold selectivity for PDE5 over PDE3, the cAMP-specific phosphodiesterase isoform involved in the control of cardiac contractility.

Two clinical studies were specifically designed to assess the time window after dosing during which sildenafil could produce an erection in response to sexual stimulation. In a penile plethysmography (RigiScan) study of fasted patients, the median time to onset for those who obtained erections of 60% rigidity (sufficient for sexual intercourse) was 25 minutes (range 12-37 minutes) on sildenafil. In a separate RigiScan study, sildenafil was still able to produce an erection in response to sexual stimulation 4-5 hours post-dose.

Sildenafil causes mild and transient decreases in blood pressure which, in the majority of cases, do not translate into clinical effects. The mean maximum decreases in supine systolic blood pressure following 100mg oral dosing of sildenafil was 8.4 mmHg. The corresponding change in supine diastolic blood pressure was 5.5 mmHg. These decreases in blood pressure are consistent with the vasodilatory effects of sildenafil, probably due to increased cGMP levels in vascular smooth muscle. Single oral doses of sildenafil up to 100mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100mg dose of sildenafil in 14 patients with severe coronary artery disease (CAD) (>70% stenosis of at least one coronary artery), the mean resting systolic and diastolic blood pressures decreased by 7% and 6% respectively compared to baseline. Mean pulmonary systolic blood pressure decreased by 9%. Sildenafil showed no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries.

No clinical relevant differences were demonstrated in time to limiting angina for sildenafil when compared with placebo in a double blind, placebo controlled exercise stress trial in 144 patients with erectile dysfunction and chronic stable angina, who were taking on a regular basis anti-anginal medications (except nitrates).

Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using the Farnsworth-Munsell 100 hue test at 1 hour following a 100mg dose, with no effects evident after 2 hours post-dose. The postulated mechanism for this change in colour discrimination is related to inhibition of PDE6, which is involved in the phototransduction cascade of the retina. Sildenafil has no effect on visual acuity or contrast sensitivity. In a small size placebo-controlled study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100mg) demonstrated no significant changes in visual tests conducted (visual acuity, Amsler grid, colour discrimination simulated traffic light, Humphrey perimeter and photostress).

There was no effect on sperm motility or morphology after single 100mg oral doses of sildenafil in healthy volunteers.

Further information on clinical trials

In clinical trials sildenafil was administered to more than 8000 patients aged 19-87. The following patient groups were represented: elderly (19.9%), patients with hypertension (30.9%), diabetes mellitus (20.3%), ischaemic heart disease (5.8%), hyperlipidaemia (19.8%), spinal cord injury (0.6%), depression (5.2%), transurethral resection of the prostate (3.7%), radical prostatectomy (3.3%). The following groups were not well represented or excluded from

clinical trials: patients with pelvic surgery, patients post-radiotherapy, patients with severe renal or hepatic impairment and patients with certain cardiovascular conditions (see section 4.3).

In fixed dose studies, the proportions of patients reporting that treatment improved their erections were 62% (25mg), 74% (50mg) and 82% (100mg) compared to 25% on placebo. In controlled clinical trials, the discontinuation rate due to sildenafil was low and similar to placebo.

Across all trials, the proportion of patients reporting improvement on sildenafil were as follows: psychogenic erectile dysfunction (84%), mixed erectile dysfunction (77%), organic erectile dysfunction (68%), elderly (67%), diabetes mellitus (59%), ischaemic heart disease (69%), hypertension (68%), TURP (61%), radical prostatectomy (43%), spinal cord injury (83%), depression (75%). The safety and efficacy of sildenafil was maintained in long term studies.

5.2 Pharmacokinetic properties

Absorption

Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} increase in proportion with dose over the recommended dose range (25-100mg).

When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution

The mean steady state volume of distribution (V_d) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.

In healthy volunteers receiving sildenafil (100mg single dose), less than 0.0002% (average 188ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Biotransformation

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-demethylation of sildenafil. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half life of approximately 4 h.

Elimination

The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half life of 3-5 h. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose).

Pharmacokinetics in special patient groups

Elderly

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency

In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min), the pharmacokinetics of sildenafil were not altered after receiving a 50mg single oral dose. The mean AUC and C_{max} of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min), sildenafil clearance was reduced, resulting in mean increases in AUC and C_{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 79% and 200% respectively.

Hepatic insufficiency

In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Povidone K29-32
Croscarmellose sodium
Magnesium stearate

Film-coating Opadry 03F20404 Blue:
Hypromellose 6cP
Titanium dioxide (E171)
Macrogol 6000
Indigo carmine, Aluminium lake (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC-PVDC/Aluminium foil blisters: 2, 4, 8 and 12 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

6th Floor

94 Wigmore Street

London

W1U 3RF

8 MARKETING AUTHORISATION NUMBER(S)

PL 24668/0144

PL 24668/0145

PL 24668/0146

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/07/2012

10 DATE OF REVISION OF THE TEXT

11/07/2012

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS PL 24668/0144-6

PATIENT INFORMATION LEAFLET

Package leaflet: Information for the patient

Sildenafil 25 mg film-coated tablets
Sildenafil 50 mg film-coated tablets
Sildenafil 100 mg film-coated tablets
Sildenafil citrate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. What Sildenafil tablets are and what they are used for
2. What you need to know before you take Sildenafil tablets
3. How to take Sildenafil tablets
4. Possible side effects
5. How to store Sildenafil tablets
6. Contents of the pack and other information

1. What Sildenafil tablets are and what they are used for

Sildenafil belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. It works by helping to relax the blood vessels in your penis, allowing blood to flow into your penis when you get sexually excited. Sildenafil tablets will only help you to get an erection if you are sexually stimulated. You should not take Sildenafil tablets if you do not have erectile dysfunction. You should not take Sildenafil tablets if you are a woman.

Sildenafil tablets are a treatment for men with erectile dysfunction, sometimes known as impotence. This is when a man cannot get, or keep a hard, erect penis suitable for sexual activity.

2. What you need to know before you take Sildenafil tablets

Do not take Sildenafil tablets:

- If you are taking medicines called nitrates, as the combination may cause a potentially dangerous decrease in your blood pressure. Tell your doctor if you are taking any of these medicines which are often given for relief of angina pectoris (or “chest pain”). If you are not certain, ask your doctor or pharmacist.
- If you are using any of the drugs known as nitric oxide donors such as amyl nitrite (“poppers”), as the combination may also lead to a potentially dangerous decrease in your blood pressure.
- If you are allergic to sildenafil or to any of the other ingredients of this medicine (listed in section 6).
- If you have a severe heart or liver problem.

- If you have recently had a stroke or a heart attack, or if you have low blood pressure.
- If you have certain rare inherited eye diseases (such as *retinitis pigmentosa*).
- If you have ever had loss of vision due to non-arteritic anterior ischaemic optic neuropathy (NAION)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Sildenafil tablets

- if you have sickle cell anaemia (an abnormality of red blood cells), leukaemia (cancer of blood cells), multiple myeloma (cancer of bone marrow).
- If you have a deformity of your penis or Peyronie's Disease.
- If you have problems with your heart. Your doctor should in that case carefully check whether your heart can take the additional strain of having sex.
- If you currently have a stomach ulcer, or a bleeding problems (such as haemophilia).
- If you experience sudden decrease or loss of vision, stop taking Sildenafil tablets and contact your doctor immediately.

You should not use Sildenafil tablets with any other oral or local treatments for erectile dysfunction.

Children and adolescents

Sildenafil tablets should not be given to individuals under the age of 18.

Special considerations for patients with kidney or liver problems

You should tell your doctor if you have kidney or liver problems. Your doctor may decide on a lower dose for you.

Other medicines and Sildenafil tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Sildenafil tablets may interfere with some medicines, especially those used to treat chest pain. In the event of a medical emergency, you should tell any health care professional treating your condition that you have taken Sildenafil tablets and when you did. Do not take Sildenafil tablets with other medicines unless your doctor tells you that you can.

You should not take Sildenafil tablets if you are taking medicines called nitrates, as the combination of these products may cause a potentially dangerous decrease in your blood pressure. Always tell your doctor or pharmacist if you are taking any of these medicines that are often used for the relief of angina pectoris (or "chest pain").

You should not take Sildenafil tablets if you are using any of the drugs known as nitric oxide donors such as amyl nitrite ("poppers") as the combination may also lead to a potentially dangerous decrease in your blood pressure.

If you are taking medicines known as protease inhibitors, such as for the treatment of HIV, your doctor may start you on the lowest dose (25 mg) of Sildenafil tablets.

Some patients who take alpha-blocker therapy for the treatment of high blood pressure or prostate enlargement may experience dizziness or light-headedness which may be caused by low blood pressure upon sitting or standing up quickly. Certain patients have

experienced these symptoms when taking Sildenafil tablets with alpha-blockers. This is most likely to occur within 4 hours after taking Sildenafil tablets. In order to reduce the likelihood that these symptoms occur, you should be on a regular daily dose of your alpha-blocker before you start Sildenafil tablets. Your doctor may start you on a lower dose (25 mg) of Sildenafil tablets.

Sildenafil tablets with food, drink and alcohol

Sildenafil tablets can be taken with or without food. However, you may find that Sildenafil tablets take longer to start working if you take them with a heavy meal. Drinking alcohol can temporarily impair your ability to get an erection. To get the maximum benefit from your medicine, you are advised not to drink excessive amounts of alcohol before taking Sildenafil tablets.

Pregnancy and breast-feeding

Sildenafil tablets are not indicated for use by women

Driving and using machines

Sildenafil tablets can cause dizziness and can affect vision. You should be aware of how you react to Sildenafil tablets before you drive or use machinery.

Sildenafil tablets contain lactose

If you have been told by your doctor that you have an intolerance to some sugars, such as lactose, contact your doctor before taking Sildenafil tablets.

3. How to take Sildenafil tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 50 mg.

You should not take Sildenafil tablets more than once a day.

You should take Sildenafil tablets about one hour before you plan to have sex. Swallow the tablet whole with a glass of water.

If you have the impression that the effect of Sildenafil is too strong or too weak, talk to your doctor or pharmacist.

Sildenafil tablets will only help you to get an erection if you are sexually stimulated. The amount of time Sildenafil tablets take to work varies from person to person, but it normally takes between half an hour and one hour. You may find that Sildenafil tablets take longer to work if you take it with a heavy meal.

If Sildenafil tablets do not help you to get an erection, or if your erection does not last long enough for you to complete sexual intercourse you should tell your doctor.

If you take more Sildenafil tablets than you should:

You may experience an increase in side effects and their severity. Doses above 100 mg do not increase the efficacy.

You should not take more tablets than your doctor tells you to.

Contact your doctor if you take more tablets than you should.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects reported in association with the use of Sildenafil tablets are usually mild to moderate and of a short duration.

If you have chest pains during or after intercourse:

- Get in a semi-sitting position and try to relax.
- **Do not use nitrates** to treat your chest pain.
- Contact your doctor immediately.

All medicines, including Sildenafil tablets can cause allergic reactions. You should contact your doctor immediately if you experience any of the following symptoms after taking Sildenafil tablets: sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.

Prolonged and sometimes painful erections have been reported after taking Sildenafil tablets. If you have an erection which lasts for more than 4 hours, you should contact a doctor immediately.

If you experience a sudden decrease or loss of vision, stop taking Sildenafil tablets and contact your doctor immediately.

A very common side effect (likely to occur in more than 1 in 10 patients) is headache.

Common side effects (likely to occur in 1 to 10 patients in 100) include: facial flushing, indigestion, effects on vision (including colour tinge to vision, light sensitivity, blurred vision or reduced sharpness of vision) stuffy nose and dizziness.

Uncommon side effects (likely to occur in 1 to 10 patients in 1000) include: vomiting, skin rash, bleeding at the back of the eye, eye irritation, bloodshot eyes /red eyes, eye pain, double vision, abnormal sensation in the eye, irregular or rapid heartbeat, muscle pain, feeling sleepy, reduced sense of touch, vertigo, ringing in the ears, nausea, dry mouth, chest pain and feeling tired.

Rare side effects (likely to occur in 1 to 10 patients in 10000) include: high blood pressure, low blood pressure, fainting, stroke, nosebleed and sudden decrease or loss of hearing.

Additional side effects reported from post-marketing experience include: pounding heartbeat, chest pain, sudden death, heart attack or temporary decreased blood flow to parts of the brain. Most, but not all, of these men had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to sildenafil. Cases of convulsions or

seizures and serious skin reactions characterised by rash, blisters, peeling skin and pain which require immediate medical attention have also been reported.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

5. How to store Sildenafil tablets

Keep this medicine out of the sight and reach of children.

Store below 30°C.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of the month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sildenafil tablets contain

- The active substance is sildenafil. Each tablet contains 25mg, 50mg or 100mg of sildenafil (as the citrate salt)
- The other ingredient(s) are: lactose monohydrate, microcrystalline cellulose, povidone K29-32, croscarmellose sodium, magnesium stearate, hypromellose 6cP, titanium dioxide (E171), macrogol 6000, indigo carmine, aluminium lake (E132).

What Sildenafil tablets look like and contents of the pack

Film-coated tablets

The 25 mg are blue elliptical, biconvex, film-coated tablets, marked "SL25" on one side.

The 50 mg are blue elliptical, biconvex, film-coated tablets, marked "SL50" on one side.

The 100 mg are blue elliptical, biconvex, film-coated tablets, marked "SL100" on one side.

The tablets are provided in blister packs containing 2, 4, 8 or 12 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Caduceus Pharma Limited
6th Floor, 94 Wigmore Street
London, W1U 3RF.

Manufacturer:

Actavis Limited
BLB 016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

This leaflet was last revised in 04/2012.

SILDENAFIL 25 MG, 50 MG & 100 MG FILM COATED TABLETS

PL 24668/0144-6

LABELLING

CARTON

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil 25mg film-coated tablets
Sildenafil 50mg film-coated tablets
Sildenafil 100mg film-coated tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 35.12mg/70.24 mg/140.48mg of sildenafil citrate corresponding to 25mg/50mg/100mg of sildenafil base

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 Film-coated tablets
4 Film-coated tablets
8 Film-coated tablets
12 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF

12. MARKETING AUTHORISATION NUMBER(S)

PL24668/0144
PL24668/0145
PL24668/0146

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

sildenafil 25mg film-coated tablets
sildenafil 50mg film-coated tablets
sildenafil 100mg film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil 25mg film-coated tablets
Sildenafil 50mg film-coated tablets
Sildenafil 100mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Caduceus Pharma Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. OTHER