Public Assessment Report

Decentralised Procedure

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

UK/H/4673/001-3/DC
UK licence numbers: PL 34771/0143-5

Macleods Pharma UK Limited
LAY SUMMARY

On 02 July 2012, the MHRA granted Macleods Pharma UK Limited Marketing Authorisations (licences) for the medicinal products, Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets (PL 34771/0143-5). 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 to get an erection if you are sexually stimulated. You should not take sildenafil if you do not have erectile dysfunction. You should not take sildenafil if you are a woman. Sildenafil is a treatment for men with erectile dysfunction, which is also 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 Macleods Pharma UK 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 (Pfizer Limited).

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.
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# Module 1

## Information about Initial Procedure

| **Product Name** | Sildenafil 25 mg film-coated tablets  
Sildenafil 50 mg film-coated tablets  
Sildenafil 100 mg film-coated tablets |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Sildenafil (as sildenafil citrate)</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>25 mg, 50 mg, 100 mg</td>
</tr>
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</table>
| **MA Holder** | Macleods Pharma UK Limited  
Golden Gate Lodge, Crewe Hall,  
Crewe, Cheshire,  
CW1 6UL,  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Germany, Hungary, Italy, Poland, Romania, Spain |
| **Procedure Number** | UK/H/4673/001-3/DC |
| **Timetable** | End of Procedure: Day 210 – 10 May 2012 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets (PL 34771/0143-5) is as follows. Differences between the individual 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
Each film-coated tablet contains sildenafil citrate equivalent to 25/50/100 mg of sildenafil.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Blue coloured, diamond shaped, film coated tablets debossed with “CL 35/36/37” on one side and plain on the other 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 film-coated Tablets to be effective, sexual stimulation is required.

4.2 Posology and method of administration
For oral use.

Use in adults
The recommended dose is 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100mg or decreased to 25mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil film-coated Tablets 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 25mg dose should be considered. Based on efficacy and toleration, the dose may be increased to 50mg and 100mg.

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.

Use in children and adolescents
Sildenafil film-coated Tablets 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.

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 film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets. 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 film-coated Tablets 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 film-coated Tablets 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 \textit{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 film-coated Tablets 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

\textit{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.

\textit{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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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, $C_{\text{max}}$, $T_{\text{max}}$, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (500mg), 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 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that Sildenafil film-coated Tablets 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 film-coated Tablets 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 film-coated Tablets, before driving or operating machinery.

4.8 Undesirable effects

The safety profile of Sildenafil film-coated Tablets is based on 8691 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 ( ≥ 1/10), common ( ≥ 1/100 to <1/10), uncommon ( ≥ 1/1,000 to <1/100), rare ( ≥ 1/10,000 to ,1/1,000).

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

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
</tr>
<tr>
<td>Very common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Somnolence, Hypoaesthesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Cerebrovascular accident, Syncope</td>
</tr>
<tr>
<td>Rare</td>
<td>Transient ischaemic attack, Seizure, Seizure recurrence</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Visual disorders, Visual colour distortion</td>
</tr>
<tr>
<td>Common</td>
<td>Conjunctival disorders, Eye disorders, Lacrimation disorders, Other eye disorders</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Non-arteritic anterior ischaemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect.</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo, Tinnitus</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations, Tachycardia</td>
</tr>
<tr>
<td>Rare</td>
<td>Deafness*</td>
</tr>
<tr>
<td>Common</td>
<td>Hypertension, Hypotension</td>
</tr>
</tbody>
</table>

### Side Effects

<table>
<thead>
<tr>
<th>Category</th>
<th>Common</th>
<th>Rare</th>
<th>Unknown</th>
<th>Not Known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion</td>
<td></td>
<td>Ventricular arrhythmia, Unstable angina, Sudden cardiac death</td>
<td>Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dyspepsia</td>
<td></td>
<td>Epistaxis</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
<td>Vomiting, Nausea, Dry mouth</td>
<td></td>
</tr>
<tr>
<td>Skin, subcutaneous and soft tissue disorders</td>
<td>Skin rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
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<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
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<tr>
<td>Uncommon</td>
<td></td>
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<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Priapism, Prolonged erection</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Not known</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chest pain, Fatigue</td>
<td></td>
<td></td>
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<tr>
<td>Uncommon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Heart rate increased</td>
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<td></td>
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</tr>
<tr>
<td>Uncommon</td>
<td></td>
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</table>

* Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trial 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 isofrom 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\text{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\text{max} of 60 minutes and a mean reduction in C\text{max} of 29%.

Distribution
The mean steady state volume of distribution (V\text{ss}) 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.

Metabolism
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\text{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\text{max} of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and C\text{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\text{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
Tablet core:
- Microcrystalline cellulose
- Calcium hydrogen phosphate dihydrate
- Croscarmellose sodium
- Hypromellose
- Magnesium stearate

Film coat:
- Hypromellose 6cP
- Titanium Dioxide (E171)
- Triacetin
- Indigo carmine Aluminum lake (E132)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
24 months

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Blister pack: Thick clear PVC (coated with 60 gsm PVdC) and Aluminium plain foil in a carton box.
Pack size: 4’s tablets

6.6 Special precautions for disposal
Any unused product should be disposed off in line with the local requirements

7 MARKETING AUTHORISATION HOLDER
Macleods Pharma UK Limited
Golden Gate Lodge, Crewe Hall,
Crewe, Cheshire,
CW1 6UL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
- PL 34771/0143
- PL 34771/0144
- PL 34771/0145

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
02/07/2012

10 DATE OF REVISION OF THE TEXT
02/07/2012
Module 3

Patient Information Leaflet

Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start taking this medicine
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Sildenafil Tablets are and what they are used for
2. Before you take Sildenafil Tablets
3. How to take Sildenafil Tablets
4. Possible side effects
5. How to store Sildenafil Tablets
6. Further information

1. WHAT SILDENAFIL TABLETS ARE AND WHAT THEY ARE USED FOR

Sildenafil Tablets belong 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 is 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. 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 (hypersensitive) to sildenafil or any of the other ingredients of Sildenafil Tablets.
- 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 because of non-arteritic anterior ischaemic optic neuropathy (NAION)

Take special care with Sildenafil Tablets
Tell your doctor
- If you have heart 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 problem (such as haemorrhoids).
- 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.

Special considerations for 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.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken other medicines, including medicines obtained without prescription.

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 healthcare 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.

Taking Sildenafil Tablets with food and drink
Sildenafil Tablets can be taken with or without food. However, you may find that Sildenafil Tablets takes longer to start working if you take it 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 is 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.
3. HOW TO TAKE SILDENAFIL TABLET

Always take Sildenafil Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are uncertain. The usual 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 Tablets 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 takes to work varies from person to person, but it normally takes between half an hour and one hour. You may find that Sildenafil Tablets takes longer to work if you take it with a heavy meal. If Sildenafil Tablets does 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. 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 or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sildenafil Tablets 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 nitrate 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 your 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):
- 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):
- Vomiting, skin rash, bleeding at the back of the eye, 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 Tablets. 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 any of the side effects get serious, or if you notice any side effects not listed in this leaflet please tell your doctor.

5. HOW TO STORE SILDENAFIL TABLET

Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions.

Do not use Sildenafil Tablets after the expiry date which is stated on the carton. The expiry date refers to the last day of the month. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Sildenafil Tablets contains

The active substance is sildenafil. Each film-coated tablet contains sildenafil citrate equivalent to 25mg, 50mg or 100mg of sildenafil.

The other ingredients are:
- Tablet Core: MCC, Calcium hydrogen phosphate, Croscarmellose sodium, Hypromellose & Magnesium stearate.

Film Coat: Hypromellose 6P, Titanium Dioxide (E171), Triacetin & Indigo carmine Aluminum lake (E132).

What do Sildenafil Tablets look like?
- 25 mg: Blue coloured, diamond shaped, film coated tablets debossed with "CL 25" on one side and plain on the other side.
- 50mg: Blue coloured, diamond shaped, film coated tablets debossed with "CL 36" on one side and plain on the other side.
- 100mg: Blue coloured, diamond shaped, film coated tablets debossed with "CL 37" on one side and plain on the other side.

What is in a pack of Sildenafil Tablets?
The tablets are provided in the blister packs containing 4 tablets.

MACLEODS
Marketing Authorisation Holder
Macleods Pharma UK Limited,
Golden Gate Lodge, Crewe Hall, Crewe,
Cheshire CW1 6UL, United Kingdom.

Manufacturer
Peckforton Pharmaceuticals Ltd.
UK Crewe Hall, Crewe, Cheshire CW1 6UL, United Kingdom.

PL 34771/0143-0145

This medicinal product is authorised in the Member States of the EEA under the following names:

United Kingdom  Sildenafil 25 mg/50 mg/100 mg film-coated tablets
Germany  Sildenafil Macleods 25 mg/50 mg/100 mg filmtabletten
Hungary  Sildenafil Macleods 25 mg/50 mg/100 mg filmtabletta
Italy  Sildenafil Macleods 25 mg/50 mg/100 mg compresse rivestite con film
Poland  Sildenafil Macleods
Romania  Sildenafil Macleods 25 mg/50 mg/100 mg comprimate filmate
Spain  Sildenafil Macleods 25 mg/50 mg/100 mg comprimidos recubiertos con película

This leaflet was last approved in (01/2012)
Module 4

Labelling

Sildenafil 25 mg film-coated tablets (PL 34771/0143)

Carton

Each tablet contains 25 mg of sildenafil (as citrate) Medicinal product subject to medical prescription. For oral use.

Read the package leaflet before use. Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions.

Braille

sildenafil # 25 mg film-coated tablets
Blister foil
Sildenafil 50 mg film-coated tablets (PL 34771/0144)

Carton

Each tablet contains 50 mg of sildenafil (as citrate). Medicinal product subject to medical prescription. For oral use.

Read the package leaflet before use. Keep out of the reach of children. This medicinal product does not require any special storage conditions.

Place dispensing label here

sildenafil
# 50 mg
film-coated tablets
Blister foil
Sildenafil 100 mg film-coated tablets (PL 34771/0145)

Carton

Barcode

Each tablet contains 100 mg of sildenafil (as citrate)
Medicinal product subject to medical prescription.
For adults.

Place dispensing label here

Braille

sildenafil
# 100 mg
film-coated tablets

sildenafil
# 100 mg
film-coated tablets
Blister foil
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Macleods Pharma UK Limited Marketing Authorisations for the medicinal products Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets (PL 34771/0143-5; UK/H/4673/001-3/DC) on 02 July 2012. The products are prescription-only medicines.

These are generic applications for Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets, submitted under Article 10(1) of Directive 2001/83 EC, as amended. The applications refer to the innovator products, Viagra ® 25 mg, 50 mg and 100 mg film-coated tablets (EU/1/98/077/002-019), authorised to Pfizer Limited since September 1998, via the centralised procedure. Viagra ® 25 mg, 50 mg and 100 mg film-coated tablets have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

With the UK as the Reference Member State (RMS) in these Decentralised Procedures, Macleods Pharma UK Limited is applying for Marketing Authorisations for Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets in Germany, Hungary, Italy, Poland, Romania and Spain.

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.

Sildenafil is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension. It is administered orally as a citrate salt although doses are expressed in terms of the base; 14 mg of sildenafil citrate is equivalent to about 10 mg of sildenafil. Sildenafil is rapidly absorbed after an oral dose, with a bioavailability of about 40%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when sildenafil is given with food. Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolized in the liver mainly by cytochrome P450 isoenzymes - CYP3A4 (the major route) and CYP2C9. The major metabolite, N-desmethyl sildenafil also has some activity. The terminal half-lives of sildenafil and the N-desmethyl metabolite are about 4 hours. Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications are for generic versions of products that have been licensed for over 10 years.

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product, Sildenafil 100mg Film-coated Tablets, to that of the reference product, Viagra ® 100 mg film-coated tablets (Pfizer Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).
The RMS 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. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS 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 of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Sildenafil 25 mg film-coated tablets  
Sildenafil 50 mg film-coated tablets  
Sildenafil 100 mg film-coated tablets |
<table>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Sildenafil citrate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Drugs used in erectile dysfunction</td>
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<td>(G04B E03)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Film-coated tablets</td>
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<td>25 mg, 50 mg, 100 mg</td>
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<tr>
<td>Reference numbers for the Decentralised Procedure</td>
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<td>DE, ES, HU, IT, PL, RO</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 34771/0143-5</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Macleods Pharma UK Limited</td>
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<td>Golden Gate Lodge, Crewe Hall,</td>
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<td>Crewe, Cheshire,</td>
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<td>United Kingdom</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Sildenafil citrate

Nomenclature:

INN: Sildenafil citrate

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

ii) 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one citrate

Structure:

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

Molecular weight: 666.7 g/mol

CAS No: 0171599-83-0

Physical form: White to off-white, crystalline powder

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

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

Synthesis of the active 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 are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging in
direct contact with the active substance complies with relevant Ph. Eur. requirements and satisfies Directive 2002/72/EC (as amended); it is suitable for 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 applied.
FINISHED PRODUCT

Description and Composition

Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets are presented as blue, diamond-shaped, film coated tablets debossed with “CL 35”/“CL 36”/“CL 37” on one side and plain on the other side. Each tablet contains 25 mg, 50 mg or 100 mg of the active ingredient, sildenafil (as sildenafil citrate).

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, calcium hydrogen phosphate dihydrate, croscarmellose sodium, hypromellose and magnesium stearate making up the tablet cores; and hypromellose 6cP, titanium dioxide (E171), triacetin 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 comply with their respective Ph Eur. monographs. The film-coating formulation complies with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

Magnesium stearate has been confirmed as being of vegetable origin. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product. None of the excipients are sourced from genetically modified organisms. There were 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, immediate-release, tablet formulations, bioequivalent to the innovator products, Viagra ® 25 mg, 50 mg and 100 mg 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 were satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and the results were satisfactory. The validation data demonstrated consistency of the manufacturing process. A commitment has been made by the MAH that full process validation will be conducted on commercial scale batches in accordance with the process validation protocol.

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 have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container Closure System

Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets are licensed for marketing in polyvinylchloride (PVC)-polyvinylidene chloride (PVdC)-aluminium foil blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in a pack size of 4 tablets.

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, using product stored in the packaging proposed for marketing. These data support the applied shelf-life of 2 years. These medicinal products do not require any special storage conditions.

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.

Product Information

The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory. Mock-ups of the PIL and labelling have been provided. The user-testing of the PIL has been evaluated and is accepted. The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets from a pharmaceutical point of view.
III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications 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. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator products, Viagra® 25 mg, 50 mg and 100 mg film-coated tablets (Pfizer Limited).

The MAH has provided adequate justification for not submitting a detailed Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. There are no environmental concerns associated with the method of manufacture or formulation of the products.

There are no objections to approval of Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INTRODUCTION

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.

INDICATIONS

Sildenafil 25mg, 50mg and 100mg 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.
POSOLOGY AND METHOD OF ADMINISTRATION

The recommended daily dose for adults 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.

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 were provided for the test and reference products.

This was an open-label, randomised, two-treatment, two-sequence, two-period, single dose crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions. Following an overnight fast, a single 100 mg dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 7 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose and at specified time points up to 24.0 hours after administration of test or reference product. Plasma levels of sildenafil and its major metabolite N-desmethyl sildenafil were detected by a validated LC-MS/MS method.

The primary pharmacokinetic parameters for the study were $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) of the ratio of the test and reference products fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for sildenafil and N-desmethyl sildenafil.

Results:

An appropriate number of subjects completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Summary pharmacokinetic data for sildenafil and N-desmethyl sildenafil for a randomised, 2-way, single-dose crossover study; healthy subjects, dosed fasted; t=24 hours. Wash-out period: 7 days.
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 $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

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/Corr), 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 are supported by the demonstration of bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of sildenafil is well-established from its extensive use 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.

CLINICAL OVERVIEW

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

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

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

Patient Information Leaflet

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

Labelling

The labelling is satisfactory.
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.
IV OVERALL CONCLUSION AND BENEFIT-RISK 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.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Sildenafil 100 mg film-coated tablets 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 mg 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.

A mock-up PIL has been provided. The package leaflet is in line with the SmPCs and is satisfactory. 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 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.

The approved labelling artwork complies with statutory requirements.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s Sildenafil 25 mg, 50 mg and 100 mg film-coated tablets are generic versions of the reference products, Viagra ® 25 mg, 50 mg and 100 mg film-coated tablets (Pfizer Limited). Extensive clinical experience with sildenafil is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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