ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sildenafil citrate equivalent to 25, 50 or 100 mg of sildenafil.

Excipient with known effect

Sildenafil Actavis 25 mg tablets
Each tablet contains 62.38 mg lactose (as monohydrate).

Sildenafil Actavis 50 mg tablets
Each tablet contains 124.76 mg lactose (as monohydrate).

Sildenafil Actavis 100 mg tablets
Each tablet contains 249.52 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Sildenafil Actavis 25 mg film-coated tablets
Sildenafil Actavis 25 mg film-coated tablets are blue elliptical, biconvex, 10.0 x 5.0 mm and marked "SL25" on one side.

Sildenafil Actavis 50 mg film-coated tablets
Sildenafil Actavis 50 mg film-coated tablets are blue elliptical, biconvex, 13.0 x 6.5 mm and marked "SL50" on one side.

Sildenafil Actavis 100 mg film-coated tablets
Sildenafil Actavis 100 mg film-coated tablets are blue elliptical, biconvex, 17.0 x 8.5 mm and marked "SL100" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sildenafil Actavis is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

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

4.2 Posology and method of administration

Posology

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

Based on efficacy and tolerability, 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 Actavis is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

Special populations

Elderly
Dosage adjustments are not required in elderly patients (≥ 65 years old).

Renal impairment
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 tolerability, the dose may be increased step-wise to 50 mg up to 100 mg as necessary.

Hepatic impairment
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25 mg dose should be considered. Based on efficacy and tolerability, the dose may be increased step-wise to 50 mg up to100 mg as necessary.

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

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

In order to minimise the potential of developing postural hypotension in patients receiving alpha-blocker treatment, patients should be stabilised 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).

Method of administration

For oral use.

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.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

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 Actavis 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.

Cardiovascular risk factors

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 Actavis 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.

Priapism

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).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO), or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors (see section 4.8). Patients should be advised that in the event of any sudden visual defect, they should stop taking Sildenafil Actavis and consult a physician immediately (see section 4.3).

Concomitant use with ritonavir

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

Concomitant use with alpha-blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration 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.

Effect on bleeding

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.

Women

Sildenafil Actavis is not indicated for use by women.

Excipents

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

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 and inducers of these isoenzymes may increase 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 25 mg should be considered.

Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg 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 200 ng/mL, compared to approximately 5 ng/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 25 mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg 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 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg 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 (500 mg 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 (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) 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 treatment 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). In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max}, respectively. Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to result in a 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 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that Sildenafil Actavis 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).

Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is 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 (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9.

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

Sildenafil (50 mg) 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 (100 mg) 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).

Addition of a single dose of sildenafil to sacubitril/valsartan at steady state in patients with hypertension was associated with a significantly greater blood pressure reduction compared to administration of sacubitril/valsartan alone. Therefore, caution should be exercised when sildenafil is initiated in patients treated with sacubitril/valsartan.

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

In healthy male volunteers, sildenafil at steady state (80 mg t.i.d.) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg b.i.d.).

4.6 Fertility, pregnancy and lactation

Sildenafil Actavis is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breast-feeding women.

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

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers (see section 5.1).

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 Actavis, before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of sildenafil is based on 9,570 patients in 74 double-blind placebo-controlled clinical studies. The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and vision blurred.

Adverse reactions from post-marketing surveillance has been gathered covering an estimated period >10 years. Because not all adverse reactions are reported the frequencies of these reactions cannot be reliably determined.

Tabulated list of adverse reactions

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)).

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 post-marketing surveillance

System Organ Class	**Very common** ***(≥ 1/10)***	**Common** ***(≥ 1/100 and <1/10)***	**Uncommon** ***(≥ 1/1000 and <1/100)***	**Rare** ***(≥ 1/10000 and <1/1000***
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	

System Organ Class	**Very common** ***(≥ 1/10)***	**Common** ***(≥ 1/100 and <1/10)***	**Uncommon** ***(≥ 1/1000 and <1/100)***	**Rare** ***(≥ 1/10000 and <1/1000***
Nervous system disorders	Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure,* Seizure recurrence,* Syncope
Eye disorders		Visual colour distortions**, Visual disturbance, Vision blurred	Lacrimation disorders***, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis	Non-arteritic anterior ischaemic optic neuropathy (NAION), * Retinal vascular occlusion,* Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration
Ear and labyrinth disorders			Vertigo, Tinnitus	Deafness

System Organ Class	**Very common** ***(≥ 1/10)***	**Common** ***(≥ 1/100 and <1/10)***	**Uncommon** ***(≥ 1/1000 and <1/100)***	**Rare** ***(≥ 1/10000 and <1/1000***
Cardiac disorders			Tachycardia, Palpitations	Sudden cardiac death,* Myocardial infarction, Ventricular arrhythmia,* Atrial fibrillation, Unstable angina
Vascular disorders		Flushing, Hot flush	Hypertension, Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis, Sinus congestion	Throat tightness, Nasal oedema, Nasal dryness
Gastrointestinal disorders		Nausea, Dyspepsia	Gastro oesophagael reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	Stevens-Johnson Syndrome (SJS),* Toxic Epidermal Necrolysis (TEN)*
Musculoskeletal and connective tissue disorders			Myalgia, Pain in extremity	
Renal and urinary disorders			Haematuria	
Reproductive system and breast disorders				Penile haemorrhage, Priapism,* Haematospermia, Erection increased
General disorders and administration site conditions			Chest pain, Fatigue, Feeling hot	Irritability

System Organ Class	Very common *(≥ 1/10)*	Common *(≥ 1/100 and <1/10)*	Uncommon *(≥ 1/1000 and <1/100)*	Rare *(≥ 1/10000 and <1/1000*
Investigations			Heart rate increased	

*Reported during post-marketing surveillance only
**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia
***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In single dose volunteer studies of doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg 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: Urologicals; Drugs used in erectile dysfunction, ATC Code: G04BE03.

Mechanism of action

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.

Pharmacodynamic 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.

Clinical efficacy and safety

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 100 mg 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 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

In a study of the hemodynamic effects of a single oral 100 mg 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.

A double-blind, placebo-controlled exercise stress trial evaluated 144 patients with erectile dysfunction and chronic stable angina who regularly received anti-anginal medicinal products (except nitrates). The results demonstrated no clinically relevant differences between sildenafil and placebo in time to limiting angina.

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 100 mg 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, 100 mg) demonstrated no significant changes in the 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 100 mg oral doses of sildenafil in healthy volunteers (see section 4.6).

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% (25 mg), 74% (50 mg) and 82% (100 mg) 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing sildenafil in all subsets of the paediatric population for the treatment of erectile dysfunction. See 4.2 for information on paediatric use.

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 (25-100 mg).

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 (100 mg single dose), less than 0.0002% (average 188 ng) 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 50 mg 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 and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film-coat:
Hypromellose
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

Sildenafil Actavis 25 mg film-coated tablets
PVC-PVDC/Aluminium blisters in cartons of 1, 2, 4, 8, 12 or 24 tablets.

Sildenafil Actavis 50 mg film-coated tablets
PVC-PVDC/Aluminium blisters in cartons of 1, 2, 4, 8, 12 or 24 tablets.

Sildenafil Actavis 100 mg film-coated tablets
PVC-PVDC/Aluminium blisters in cartons of 1, 2, 4, 8, 12 or 24 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Sildenafil Actavis 25 mg film-coated tablets
EU/1/09/595/001
EU/1/09/595/002
EU/1/09/595/003
EU/1/09/595/004
EU/1/09/595/005
EU/1/09/595/016

Sildenafil Actavis 50 mg film-coated tablets
EU/1/09/595/006
EU/1/09/595/007
EU/1/09/595/008
EU/1/09/595/009
EU/1/09/595/010
EU/1/09/595/017

Sildenafil Actavis 100 mg film-coated tablets
EU/1/09/595/011
EU/1/09/595/012
EU/1/09/595/013
EU/1/09/595/014
EU/1/09/595/015
EU/1/09/595/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 December 2009
Date of latest renewal: 4 September 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Actavis Ltd.
BLB 015-016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 25 mg film-coated tablets
sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sildenafil citrate equivalent to 25 mg of sildenafil.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 film-coated tablet
2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
24 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/595/001 [1 film-coated tablet]
EU/1/09/595/002 [2 film-coated tablets]
EU/1/09/595/003 [4 film-coated tablets]
EU/1/09/595/004 [8 film-coated tablets]
EU/1/09/595/005 [12 film-coated tablets]
EU/1/09/595/016 [24 film-coated tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sildenafil Actavis 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 25 mg tablets
sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 50 mg film-coated tablets
sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sildenafil citrate equivalent to 50 mg of sildenafil.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 film-coated tablet
2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
24 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/595/006 [1 film-coated tablet]
EU/1/09/595/007 [2 film-coated tablets]
EU/1/09/595/008 [4 film-coated tablets]
EU/1/09/595/009 [8 film-coated tablets]
EU/1/09/595/010 [12 film-coated tablets]
EU/1/09/595/017 [24 film-coated tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sildenafil Actavis 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 50 mg tablets
sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 100 mg film-coated tablets
sildenafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sildenafil citrate equivalent to 100 mg of sildenafil.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 film-coated tablet
2 film-coated tablets
4 film-coated tablets
8 film-coated tablets
12 film-coated tablets
24 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/595/011 [1 film-coated tablet]
EU/1/09/595/012 [2 film-coated tablets]
EU/1/09/595/013 [4 film-coated tablets]
EU/1/09/595/014 [8 film-coated tablets]
EU/1/09/595/015 [12 film-coated tablets]
EU/1/09/595/018 [24 film-coated tablets]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sildenafil Actavis 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Sildenafil Actavis 100 mg tablets
sildenafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sildenafil Actvis 25 mg, 50 mg and 100 mg film-coated tablets
Sildenafil Actavis 25 mg film-coated tablets
Sildenafil Actavis 50 mg film-coated tablets
Sildenafil Actavis 100 mg film-coated tablets
sildenafil

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, 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. See section 4.

What is in this leaflet

1. What Sildenafil Actavis is and what it is used for

Sildenafil Actavis contains the active substance sildenafil which 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 Actavis will only help you to get an erection if you are sexually stimulated.
Sildenafil Actavis is a treatment for adult 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 Actavis

Do not take Sildenafil Actavis

- If you are allergic to sildenafil or any of the other ingredients of this medicine (listed in section 6).

- If you are taking medicines called nitrates, as the combination may lead to a dangerous fall 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 medicines known as nitric oxide donors such as amyl nitrite (“poppers”), as the combination may also lead to a dangerous fall in your blood pressure.

- If you are taking riociguat. This drug is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors, such as Sildenafil Actavis have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

- 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 Actavis

- 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 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 Actavis and contact your doctor immediately.

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

You should not use Sildenafil Actavis with treatments for pulmonary arterial hypertension (PAH) containing sildenafil or any other PDE5 inhibitors.

You should not take Sildenafil Actavis if you do not have erectile dysfunction.

You should not take Sildenafil Actavis if you are a woman.

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.

Children and adolescents
Sildenafil Actavis should not be given to individuals under the age of 18.

Other medicines and Sildenafil Actavis

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

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

You should not take Sildenafil Actavis if you are taking medicines called nitrates, as the combination of these medicines may lead to a dangerous fall in your blood pressure. Always tell your doctor, pharmacist or nurse 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 Actavis if you are using any of the medicines known as nitric oxide donors such as amyl nitrite ("poppers") as the combination may also lead to a dangerous fall in your blood pressure.

Tell your doctor or pharmacist if you are already taking riociguat.

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 Actavis.

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 with alpha-blockers. This is most likely to happen within 4 hours after taking Sildenafil Actavis. To reduce the chance that these symptoms might happen, you should be on a regular daily dose of your alpha-blocker before you start Sildenafil Actavis. Your doctor may start you on a lower dose (25 mg) of Sildenafil Actavis.

Tell your doctor or pharmacist if you are already taking medicines containing sacubitril/valsartan, used to treat heart failure.

Sildenafil Actavis with food and drink and alcohol
Sildenafil Actavis can be taken with or without food. However, you may find that Sildenafil Actavis 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 Actavis.

Pregnancy, breast-feeding and fertility
Sildenafil Actavis is not indicated for use by women.

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

Sildenafil Actavis contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

3. How to take Sildenafil Actavis

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 Actavis more than once a day.

You should take Sildenafil Actavis about one hour before sexual activity. Swallow the tablet whole with a glass of water.

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

Sildenafil Actavis will only help you to get an erection if you are sexually stimulated. The amount of time Sildenafil Actavis takes to work varies from person to person, but it normally takes between half

an hour and one hour. You may find that Sildenafil Actavis takes longer to work if you take it with a heavy meal.

If Sildenafil Actavis 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 Actavis 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 are usually mild to moderate and of a short duration.

If you experience any of the following serious side effects stop taking Sildenafil Actavis and seek medical help immediately:

- An allergic reaction - this occurs **uncommonly** (may affect up to 1 in 100 people)
  Symptoms include sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat.

- Chest pains - this occurs **uncommonly**
  If this occurs during or after intercourse
  - Get in a semi-sitting position and try to relax.
  - **Do not use nitrates** to treat your chest pain.

- Prolonged and sometimes painful erections - this occurs **rarely** (may affect up to 1 in 1,000 people)
  If you have an erection which lasts for more than 4 hours, you should contact a doctor immediately.

- A sudden decrease or loss of vision - this occurs **rarely**

- Serious skin reactions - this occurs **rarely**
  Symptoms may include severe peeling and swelling of the skin, blistering of the mouth, genitals and around the eyes, fever.

- Seizures or fits - this occurs **rarely**

Other side effects:

Very common (may affect more than 1 in 10 people): headache.

Common (may affect up to 1 in 10 people): nausea, facial flushing, hot flush (symptoms include a sudden feeling of heat in your upper body), indigestion, colour tinge to vision, blurred vision, visual disturbance, stuffy nose and dizziness.

Uncommon (may affect up to 1 in 100 people): vomiting, skin rash, eye irritation, bloodshot eyes /red eyes, eye pain, seeing flashes of light, visual brightness, light sensitivity, watery eyes, pounding heartbeat, rapid heartbeat, high blood pressure, low blood pressure, muscle pain, feeling sleepy, reduced sense of touch, vertigo, ringing in the ears, dry mouth, blocked or stuffy sinuses, inflammation of the lining of the nose (symptoms include runny nose, sneezing and stuffy nose), upper abdominal pain, gastro-oesophageal reflux disease (symptoms include heartburn), presence of blood in urine, pain in the arms or legs, nosebleed, feeling hot and feeling tired.

Rare (may affect up to 1 in 1,000 people): fainting, stroke, heart attack, irregular heartbeat, temporary decreased blood flow to parts of the brain, feeling of tightening of the throat, numb mouth, bleeding at the back of the eye, double vision, reduced sharpness of vision, abnormal sensation in the eye, swelling of the eye or eyelid, small particles or spots in your vision, seeing halos around lights, dilation of the pupil of the eye, discolouration of the white of the eye, penile bleeding, presence of blood in semen, dry nose, swelling of the inside of the nose, feeling irritable and sudden decrease or loss of hearing.

From post-marketing experience cases of unstable angina (a heart condition) and sudden death have been reported rarely. Of note, most, but not all, of the men who experienced these side effects had heart problems before taking this medicine. It is not possible to determine whether these events were directly related to sildenafil.

Reporting of side effects
If you get any side effects, talk to you doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sildenafil Actavis

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

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

Store below 30°C.

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

What Sildenafil Actavis looks like and contents of the pack

Film-coated tablet

Sildenafil Actavis 25 mg film-coated tablets are blue elliptical, biconvex, 10.0 x 5.0 mm and marked "SL25" on one side.
Sildenafil Actavis 50 mg film-coated tablets are blue elliptical, biconvex, 13.0 x 6.5 mm and marked "SL50" on one side.
Sildenafil Actavis 100 mg film-coated tablets are blue elliptical, biconvex, 17.0 x 8.5 mm and marked "SL100" on one side.

The tablets are provided in blister packs containing 1, 2, 4, 8, 12 or 24 tablets.

Some pack sizes may not be marketed in your country.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

Manufacturer
Actavis Ltd.
BLB 015-016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Teva Pharma Belgium N.V./S.A./AG
Tél/Tel: +32 38207373

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Tel: +34 913873280

France
Teva Santé
Tél: +33 155917800

Hrvatska
Pliva Hrvatska d.o.o.
Tel: +385 13720000

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Tel: +44 2075407117

Ísland
Teva Pharma Iceland ehf.
Sími: +354 5503300

Italia
Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος
Specifar A.B.E.E.
Ελλάδα
Τηλ: +30 2118805000

Latvija
UAB Teva Baltics filiāle Latvijā
Tel: +371 67323666

Österreich
ratiopharm Arzneimittel Vertriebs-GmbH
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Teva Pharmaceuticals Polska Sp. z o.o.
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Tel: +351 214767550

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Teva Pharmaceuticals S.R.L.
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Slovenija
Pliva Ljubljana d.o.o.
Tel: +386 15890390

Slovenská republika
TEVA Pharmaceuticals Slovakia s.r.o.
Tel: +421 257267911

Suomi/Finland
Teva Finland Oy
Puh/Tel: +358 201805900

Sverige
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United Kingdom (Northern Ireland)
Teva Pharmaceuticals Ireland
Ireland
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This leaflet was last revised in {MM/YYYY}.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.