

1 NAME OF THE MEDICINE

Sildenafil (as citrate).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sildenafil citrate is an orally active selective inhibitor of cGMP - specific PDE5 (phosphodiesterase type 5) which is the predominant PDE isoenzyme in human corpora cavernosa.

VEDAFIL film coated tablets contain 25, 50 or 100 mg sildenafil (as citrate) as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

VEDAFIL (Sildenafil (as citrate)) : Blue film-coated, round biconvex tablets debossed with 'M' on one side and 'SL over 25' on other side.
25 mg tablets

VEDAFIL (Sildenafil (as citrate)) : Blue film-coated, round biconvex tablets debossed with 'M' on one side and 'SL over 50' on other side.
50 mg tablets

VEDAFIL (Sildenafil (as citrate)) : Blue film-coated, round biconvex tablets debossed with 'M' on one side and 'SL over 100' on other side.
100 mg tablets

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VEDAFIL is indicated for the treatment of erectile dysfunction in adult males.

VEDAFIL is not indicated for use by women.

4.2 DOSE AND METHOD OF ADMINISTRATION

Sildenafil citrate tablets are for oral administration.

Use in Adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on the efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day.

Dosage Adjustment in Renal Impairment

The dosing recommendations for Use in Adults should be followed for patients with mild to moderate renal impairment ($Cl_{cr} = 30-80$ mL/min).

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

Dosage Adjustment in Hepatic Impairment

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

Dosage Adjustment in the Elderly

Since sildenafil clearance is reduced in elderly patients, a first dose of 25 mg should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg and 100 mg.

Use in Patients Using Other Medicines

Concomitant use of potent CYP 3A4 inhibitors has been associated with increased plasma levels of sildenafil (e.g., erythromycin, 182%, saquinavir, 210%). It can also be expected that more potent CYP 3A4 inhibitors such as ketoconazole and itraconazole would result in increased plasma levels of sildenafil (see SECTION 4.8 ADVERSE EFFECTS - Effects of Other Medicines on Sildenafil Citrate). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir, it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48 hour period (see SECTION 4.8 ADVERSE EFFECTS - Effects of Other Medicines on Sildenafil Citrate).

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 lower doses should be considered (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and SECTION 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.).

Use in Children

Sildenafil citrate is not indicated for use in children.

4.3 CONTRAINDICATIONS

Use of sildenafil citrate is contraindicated in patients with known hypersensitivity to any component of the tablet.

Nitrates and sildenafil citrate must not be used concomitantly. Sildenafil citrate was shown to potentiate the hypotensive effects of both acute and chronic nitrate administration and therefore, its co-administration with nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently is contraindicated. Drugs which must not be used concomitantly include glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form.

The co-administration of PDE5 inhibitors, including VIAGRA, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

Sildenafil citrate is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors (e.g. patients with severe cardiovascular disease such as established cardiac failure and unstable angina pectoris) (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing sildenafil citrate.

Sildenafil citrate is not recommended in patients with male erectile dysfunction with a previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing Experience).

The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), hypertension (blood pressure >170/110 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 thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, including those with recent onset angina, since there is a degree of cardiovascular risk associated with sexual intercourse. Sildenafil citrate has vasodilator properties, resulting in mild and transient decreases in blood pressure and, as such, potentiates the hypotensive effect of nitrates (see SECTION 4.3 CONTRAINDICATIONS).

Physicians should advise patients to stop use of all PDE5 inhibitors, including sildenafil citrate, and seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely post marketing in temporal association with the use of all PDE-5 inhibitors. An observational study evaluating whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION suggests an increase in the risk of NAION with PDE5 inhibitor use. In case of sudden visual loss, patients should be advised to stop taking sildenafil and consult a physician immediately.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. PDE 5 inhibitors, including sildenafil, are not recommended in patients with male erectile dysfunction with a previous episode of NAION (see SECTION 4.3 CONTRAINDICATIONS and SECTION 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post Marketing Experience).

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure (see SECTION 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Trials). This is of little or no consequence in most patients. However, 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.

Agents for the treatment of erectile dysfunction 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 leukemia).

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

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 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at lower doses should be considered (see SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

Sildenafil citrate had no effect on bleeding time, including during co-administration with aspirin. In-vitro studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of sildenafil citrate to patients with bleeding disorders or active peptic ulceration. Therefore, sildenafil citrate should be administered with caution to these patients.

There are limited safety data in patients with diabetic retinopathy. The safety of sildenafil citrate in patients with untreated diabetic retinopathy has not been studied and therefore sildenafil citrate should be administered to these patients only after careful benefit-risk assessment.

Sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

The incidence of adverse events may be greater in those patients who require the maximum recommended dose of 100 mg (e.g. some diabetic and spinal cord injury patients).

Patients with cardiovascular disease who have not engaged in sexual intercourse for a number of years should have their cardiovascular status carefully assessed prior to initiating treatment with sildenafil citrate.

Prolonged erections greater than four hours in duration and priapism (painful erections greater than 6 hours) have been reported infrequently since market approval of sildenafil citrate. 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.

Use in the Elderly

No data available

Paediatric Use

No data available

Effects on Laboratory Tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of Other Medicines on Sildenafil Citrate

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.

Population pharmacokinetics analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). However, there was no increased incidence of adverse events in these patients.

Cimetidine (800 mg), a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil citrate (50 mg) to healthy volunteers.

When a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg B.I.D. for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC).

Coadministration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) with sildenafil citrate (100 mg single dose) resulted in a 140% increase in sildenafil C_{max} and a 210% increase in sildenafil AUC. (See SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION). Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have still greater effects.

Coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} .

and a 1000% (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 dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. (See SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION).

Since systemic exposure to sildenafil increases on co-administration with inhibitors of CYP3A4 the sildenafil citrate dose may have to be reduced depending on tolerability.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampicin, will decrease plasma levels of sildenafil.

Population pharmacokinetics analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors, CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, ACE inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as 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. Sildenafil (80 mg three times a day) increased bosentan AUC and C_{max} by 49.8% and 42%, respectively.

Riociguat: Preclinical studies showed an 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 sildenafil. 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 as it may potentially lead to symptomatic hypotension (see SECTION 4.3 CONTRAINDICATIONS).

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

There is no information on the interaction between sildenafil and ciclosporin.

Effects of Sildenafil Citrate on Other Medicines

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 citrate 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 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 lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. (See SECTION 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE and SECTION 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 citrate (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

Sildenafil causes a small reduction in supine and tilted diastolic blood pressure (3.5 and 6.1 mmHg respectively) in healthy subjects who had a blood alcohol level of 80 mg/dL.

No interaction was seen when sildenafil citrate (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additive reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when sildenafil citrate was administered alone to healthy volunteers (see SECTION 5.1 PHARMACODYNAMIC PROPERTIES).

Analysis of the safety data base showed no difference in the side effect profile in patients taking sildenafil citrate with and without anti-hypertensive medication.

Sildenafil citrate was shown to potentiate the hypotensive effect of acute and chronic nitrate administration. Therefore, use of nitric oxide donors, organic nitrates, or organic nitrites in any form either regularly or intermittently with sildenafil citrate is contraindicated (see SECTION 4.3 CONTRAINDICATIONS).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There was no impairment of fertility in rats given sildenafil for 36 days to females and 102 days to males at a dose producing an AUC value of more than 25 times the human male AUC.

There is no information on the effects of sildenafil on semen production, sperm motility/morphology in patients suffering from erectile dysfunction. There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil citrate in healthy volunteers.

Use in Pregnancy

Pregnancy Category: B1

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Sildenafil citrate is not indicated for use by women.

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. The dose results in total systemic drug exposure (AUC) for unbound sildenafil and its major metabolite of greater than 60 times the exposure observed in human males given the maximum recommended human dose (MRHD) of 100 mg. In the rat pre- and post natal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well controlled studies of sildenafil in pregnant women.

Use in Lactation

Sildenafil citrate is not indicated for use in women. No information is available on its secretion into breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As transient visual disturbances and dizziness have been reported in some patients taking sildenafil citrate, particularly at the 100 mg dose, patients should be aware of how they react to sildenafil citrate before driving or operating machinery, and the doctor should advise accordingly.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Sildenafil citrate was administered to over 3700 patients (aged 19-87) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

Treatment with sildenafil citrate was well tolerated. In placebo controlled clinical studies, the discontinuation rate due to adverse events was low and similar to placebo. The adverse events were generally transient and mild to moderate in nature.

Across trials of all designs, the profile of adverse events reported by patients receiving sildenafil citrate was similar. In fixed dose studies, the incidence of adverse events increased with dose. The nature of the adverse events in flexible dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed dose studies.

When sildenafil citrate was taken as recommended (on an as needed basis in flexible dose placebo controlled clinical trials) the following adverse events were reported:

| Table 1. Adverse events reported by $\geq 2\%$ of patients treated with sildenafil citrate or placebo in PRN flexible dose phase II/III studies | | |
|---|---|----------------------------|
| Adverse event | Percentage of patients reporting event | |
| | Sildenafil citrate (N=734) | PLACEBO (N=725) |
| Headache | 16% | 4% |
| Flushing | 10% | 1% |
| Dyspepsia | 7% | 2% |
| Nasal Congestion | 4% | 2% |
| Urinary Tract Infection | 3% | 2% |
| Abnormal Vision ⁺ | 3% | 0% |
| Diarrhoea | 3% | 1% |
| Dizziness | 2% | 1% |
| Rash | 2% | 1% |

+ Abnormal Vision: Mild and transient predominantly colour tinge to vision, but also increased perception to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision. This effect was more common at doses of 100 mg or more.

Other adverse reactions occurred at a rate of $>2\%$, but equally commonly on placebo: respiratory tract infection, back pain, flu syndrome and arthralgia.

In fixed dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses.

At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

No cases of priapism were reported during controlled clinical trials.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to sildenafil citrate is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

General disorders and administrative site conditions: face oedema, oedema, peripheral oedema, asthenia, pain, chills, chest pain, thirst.

Immune systems disorders: hypersensitivity.

Cardiac Disorders: angina pectoris, AV block, tachycardia, palpitation, myocardial ischaemia, cardiac arrest, heart failure, cardiomyopathy.

Vascular disorders: hypotension, postural hypotension, vasodilation, shock.

Gastrointestinal Disorders: nausea, vomiting, glossitis, colitis, dysphagia, gastritis, oesophagitis, stomatitis, dry mouth, rectal haemorrhage, abdominal pain.

Blood and lymphatic systems disorders: anaemia and leukopenia.

Metabolic and nutritional disorders: gout, unstable diabetes, hyperglycaemia, hyperuricemia, hypoglycaemic reaction, hypernatremia.

Musculoskeletal and connective tissue disorders: arthritis, arthrosis, myalgia, tenosynovitis, bone pain, myasthenia, synovitis.

Injury, poisoning and procedural complications: accidental fall, accidental injury, tendon rupture.

Nervous system disorders: ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, vertigo, somnolence, hyporeflexia, hypaesthesia, migraine, syncope, cerebral thrombosis.

Psychiatric disorders: depression, insomnia, abnormal dreams.

Respiratory thoracic and mediastinal disorders: respiratory disorder, asthma, dyspnoea, sputum increased, cough increased.

Infections and infestations: infection, rhinitis, sinusitis, bronchitis, laryngitis, pharyngitis, herpes simplex, gastroenteritis, gingivitis, cystitis.

Skin and subcutaneous tissue disorders: urticaria, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis, photosensitivity reaction

Eye disorders: mydriasis, conjunctivitis, photophobia, eye pain, eye haemorrhage, cataract, dry eyes.

Ear and labyrinth disorders: sudden decrease or loss of hearing, ear pain, tinnitus.

Reproductive and breast disorders: prostatic disorder, breast enlargement, abnormal ejaculation, genital oedema and anorgasmia.

Renal and urinary disorders: nocturia, urinary frequency, urinary incontinence.

Investigations: abnormal electrocardiogram, liver tests abnormal.

Adverse reactions reported in clinical trials that are not included in the above section include:

Eye disorders: visual disturbance, cyanopsia, photopsia, chromatopsia, ocular hyperaemia, visual brightness, eye oedema, eye swelling, dry eye, asthenopia, halo vision, xanthopsia, erythroptosis, eye disorder, conjunctival hyperaemia, eye irritation, abnormal sensation in eye, eyelid oedema.

Vascular disorders: hot flush.

Respiratory, thoracic and mediastinal disorders: sinus congestion, epistaxis, throat tightness, nasal dryness, nasal oedema.

Gastrointestinal disorders: gastro-oesophageal reflux disease, hypoaesthesia oral.

Musculoskeletal and connective tissue disorders: pain in extremity.

Reproductive system and breast disorders: erection increased.

General disorders and administration site conditions: feeling hot, irritability.

Investigations: heart rate increased.

Post Marketing Experience

Cardiac disorders and vascular disorders: serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack and hypertension, have been reported post marketing in temporal association with the use of sildenafil citrate. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil citrate without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil citrate and sexual activity. It is not possible to determine whether these events are related directly to sildenafil citrate, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

Tachycardia, hypotension, syncope, and epistaxis have also been reported post marketing. Rare spontaneous reports have been received of hypotensive events after the use of sildenafil in combination with alpha blockers.

Other events reported post marketing to have been observed in temporal association with sildenafil citrate and not listed in the clinical trials adverse reactions section include:

Nervous system disorders: seizure, seizure recurrence and anxiety

Reproductive system and breast disorders: priapism and prolonged erection

Renal disorders: haematuria.

Eye disorders: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema.

Non-arteritic anterior ischaemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil citrate. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking. An observational study evaluating whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION suggests an increase in the risk of NAION with PDE5 inhibitor use (see SECTION 4.3 CONTRAINDICATIONS and SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Immune system disorders: hypersensitivity reaction.

Ear and labyrinth disorders: Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including sildenafil citrate. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether

these reported events are related directly to the use of sildenafil citrate, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors (see SECTION 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose information is limited. In studies with healthy volunteers, of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Sildenafil blood levels are not clinically useful. Monitor ECG and blood pressure in symptomatic patients. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Sildenafil citrate is an oral therapy for erectile dysfunction, which restores impaired erectile function by increasing blood flow to the penis, resulting in a natural response to sexual stimulation.

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) which is responsible for degradation of cGMP in the corpus cavernosum. Sildenafil citrate 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 citrate to produce its beneficial pharmacological effects.

Single oral doses of sildenafil citrate up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. The mean maximum decreases in supine systolic blood pressure following 100 mg oral dosing 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.

Sildenafil citrate has no effect on visual acuity or contrast sensitivity. Mild and transient differences in colour discrimination (blue/green) were detected in some subjects using 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. In-vitro studies show that sildenafil is ten-fold less potent against PDE6 than PDE5.

Human platelets contain PDE5 enzyme system. Sildenafil, in limited studies, did not affect platelet function *in vivo*. In in-vitro studies, sildenafil was shown to potentiate the antiaggregatory effect of the nitric oxide donor, sodium nitroprusside.

Studies *in vitro* have shown that sildenafil has between 10 and 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms (PDEs 1, 2, 3, 4, 6, 7 to 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 Trials

The efficacy and safety of sildenafil citrate was evaluated in 21 randomised, double-blind placebo controlled trials up to 6 months duration. Sildenafil citrate was administered to more than 3,000 patients aged 19-87, with erectile dysfunction of various aetiologies (organic, psychogenic, mixed). The efficacy was evaluated by global assessment questions, diary of erections, the International Index of Erectile Function (IIEF, a validated sexual function questionnaire) and a partner questionnaire.

Sildenafil citrate efficacy, determined as the ability to achieve and maintain an erection sufficient for sexual intercourse, was demonstrated in all 21 studies and was maintained in long term extension studies (one year). In fixed dose studies the proportions of patients reporting that treatment improved their erections were 62% (25 mg), 74% (50 mg), 82% (100 mg) compared to 25% on placebo. In addition to improvements in erectile function, analysis of IIEF showed that sildenafil citrate treatment also improved the domains of orgasm, satisfaction with intercourse and overall satisfaction.

Across all trials, the proportion of patients reporting improvement on sildenafil citrate were 59% of diabetic patients, 43% of radical prostatectomy patients and 83% of patients with spinal cord injury (versus 16%, 15% and 12% on placebo respectively).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Sildenafil is rapidly absorbed after oral administration. 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%). The oral pharmacokinetics of sildenafil are proportional over the recommended dose range (25 mg-100 mg).

When sildenafil citrate is taken with a high fat meal, 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%. Patients may need to individualise their dosing relative to their food intake based on their own experienced clinical response.

Distribution

The mean steady state volume of distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

In sixteen healthy volunteers receiving sildenafil citrate (100 mg single dose), the mean semen concentrations of sildenafil 1.5 and 4 hours post dose were 18% and 17% respectively of the plasma concentration at the same time point. The amount in the ejaculate at 90 minutes after dosing was less than 0.0002% of the administered dose.

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 PDE selectivity profile similar to sildenafil and an *in-vitro* potency for PDE5 approximately 50% 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.

Excretion

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the faeces

(approximately 80% of administered oral dose) 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, with free plasma concentrations approximately 40% greater than those seen in younger volunteers (18-45 years). However, analysis of the safety database showed that age had no effect on the incidence of adverse events.

Renal insufficiency

In volunteers with mild ($Cl_{cr} = 50-80$ mL/min) and moderate ($Cl_{cr} = 30-49$ mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil citrate (50 mg) were not altered. In volunteers with severe ($Cl_{cr} = \leq 30$ mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C_{max} (88%) compared to age-matched volunteers with no renal impairment.

Hepatic insufficiency

In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severe hepatic impairment have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Sildenafil was negative in *in-vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in-vitro* human lymphocytes and *in-vivo* mouse micronucleus assays to detect clastogenicity.

Carcinogenicity

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUC) for unbound sildenafil and its major metabolite of 35- and 39-times, for male and female rats, respectively, the exposures observed in human males given the maximum recommended human dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the maximum tolerated dose of 10 mg/kg/day, but resulting in total systemic drug exposure for unbound sildenafil and its major metabolite of less than the exposures observed in human males given the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VEDAFIL tablets contains the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, magnesium stearate and OPADRY complete film coating system 03K80846 BLUE (ARTG PI No: 106239).

6.2 INCOMPATIBILITIES

Please refer to SECTION 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container

6.5 NATURE AND CONTENTS OF CONTAINER

- VEDAFIL 25 mg tablets : Packed in * PVC/Aluminium blisters packs of 1, 4 or 8 tablets.
- VEDAFIL 50 mg tablets : Packed in * PVC/Aluminium blisters packs of 1, 3, 4, 8 or 12 tablets.
- VEDAFIL 100 mg tablets : Packed in *PVC/Aluminium blisters packs of 1, 4, 8 or 12 tablets.

*Not all pack sizes may be marketed in Australia

Australian Register of Therapeutic Goods (ARTG)

AUST R 162805 – VEDAFIL sildenafil (as citrate) 50 mg film-coated tablet blister pack

AUST R 162806 – VEDAFIL sildenafil (as citrate) 100 mg film-coated tablet blister pack

AUST R 162807 – VEDAFIL sildenafil (as citrate) 25 mg film-coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

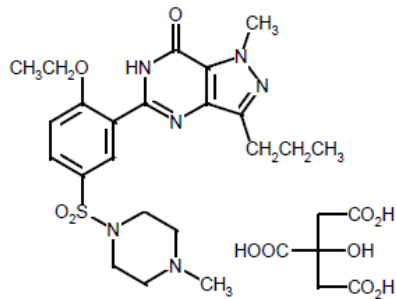
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine citrate

Structural formula:



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

Molecular weight: 666.7

CAS Number

171,599-83-0

Sildenafil citrate is a off-white, crystalline powder. Its aqueous solubility is equivalent to 2.6 mg sildenafil per mL at 25°C.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription only medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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30-34 Hickson Road
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www.viatris.com.au
Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

27/05/2010

10 DATE OF REVISION

13/07/2022

Summary Table of Changes

| Section Changed | Summary of New Information |
|-----------------|----------------------------|
| All | Minor editorial changes |
| 2 | Minor editorial update |
| 6.5 | Insert AUST R numbers |
| 8 | Update sponsor's details |

VEDAFIL® is a Viatris company trade mark

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