

## **PRODUCT MONOGRAPH**

### **Pr Dom-SILDENAFIL**

Sildenafil Citrate Tablets

25 mg, 50 mg and 100 mg sildenafil (as sildenafil citrate)

cGMP-Specific Phosphodiesterase Type 5 Inhibitor

Treatment of Erectile Dysfunction

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## Pr Dom-SILDENAFIL

Sildenafil Citrate Tablets

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	25 mg, 50 mg and 100 mg Tablets	Lactose  <i>* For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

#### INDICATIONS AND CLINICAL USE

Dom-SILDENAFIL (sildenafil citrate) is indicated for:

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

#### CONTRAINDICATIONS

Sildenafil citrate has been shown to potentiate the hypotensive effects of nitrates in healthy volunteers and in patients, and is therefore contraindicated in patients who are taking any type of nitrate drug therapy, or who utilize short-acting nitrate-containing medications, due to the risk of developing potentially life-threatening hypotension. The use of organic nitrates, either regularly and/or intermittently, in any form (e.g. oral, sublingual, transdermal, by inhalation) is absolutely contraindicated (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

After patients have taken sildenafil citrate, it is unknown when nitrates, if necessary, can be safely administered. Plasma levels of sildenafil at 24 hours post-dose are much lower (2 ng/mL) than at peak concentration (440 ng/mL). In the following patients: age >65, hepatic impairment (e.g. cirrhosis), severe renal impairment (e.g.  $CL_{cr} < 30$  mL/min), and concomitant use of potent cytochrome P-450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post-dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post-dose are much lower than at peak concentration, it is unknown

whether nitrates can be safely coadministered at this time point (see **DETAILED PHARMACOLOGY, Pharmacodynamic Studies**).

Treatments for erectile dysfunction should not be generally used in men for whom sexual activity is inadvisable (see also **WARNINGS AND PRECAUTIONS**).

Dom-SILDENAFIL is contraindicated in patients with a known hypersensitivity to any component of the tablet (see **PHARMACEUTICAL INFORMATION**).

## **WARNINGS AND PRECAUTIONS**

### **General**

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

### **Cardiovascular**

As with all treatments for erectile dysfunction, there is a potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease, including hypertension (BP>140/90). Therefore, treatments for erectile dysfunction, including sildenafil citrate, should not be generally administered in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

There are no controlled clinical data on the safety or efficacy of sildenafil citrate in the following groups, if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months
- Patients with resting hypotension (BP <90/50 at rest) or hypertension (BP >170/110 at rest)
- Patients with cardiac failure or coronary artery disease causing unstable angina (see **ACTION AND CLINICAL PHARMACOLOGY**).

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the coadministration may lead to symptomatic hypotension in a few susceptible individuals (see **DRUG INTERACTIONS**). In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at lower doses should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

### **Hematologic**

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure (see **DETAILED PHARMACOLOGY**). 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.

In humans, sildenafil citrate has no effect on bleeding time when taken alone or with acetylsalicylic acid. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and sildenafil citrate had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans (see **ACTION AND CLINICAL PHARMACOLOGY**).

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.

### **Hepatic/Biliary/Pancreatic**

In volunteers with 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.

A starting dose of 25 mg should be considered in patients with hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

### **Ophthalmologic**

Postmarketing reports of sudden loss of vision have occurred rarely, in temporal association with the use of PDE5 inhibitors. It is not clear whether these are related directly to the use of PDE5 inhibitors or to other factors. There may be an increased risk to patients who have already experienced Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION).

There are no controlled clinical data on the safety or efficacy of sildenafil citrate in patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases). If prescribed, this should be done with caution. (see **ACTION AND CLINICAL PHARMACOLOGY**).

A small percentage of patients experience visual effects (e.g. impairment of colour discrimination, increased perception to light, blurred vision, eye pain, ocular redness) after taking sildenafil citrate. If this happens, then the patient should not operate a motor vehicle or any heavy machinery until the adverse effects disappear (see **ACTION AND CLINICAL PHARMACOLOGY**).

Rare cases of central serous chorioretinopathy have been reported during the post-marketing period in temporal association with the use of sildenafil citrate. It is not known if medical and other facts were reported that may have also played a role in the development of the condition. It is not possible to determine whether the development of the condition was related directly to the use of sildenafil, to the patient's possible underlying risk factors, a combination of these factors, or to other factors. These cases of central serous chorioretinopathy in patients receiving sildenafil did not provide evidence of serious or permanent alteration in visual function. (See **POST-MARKET ADVERSE DRUG REACTIONS**).

### **Otologic**

Sudden decrease or loss of hearing has been reported in a few number of postmarketing and clinical trials cases with the use of PDE5 inhibitors, including sildenafil citrate. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake 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 events are related directly to the use of PDE5 inhibitors or to other factors (see **ADVERSE REACTIONS, POST-MARKET ADVERSE DRUG REACTIONS and PART III CONSUMER INFORMATION**). Physicians should advise patients to stop taking sildenafil citrate and seek prompt medical attention in case of sudden decrease or loss of hearing.

### **Renal**

In volunteers with mild (CL<sub>cr</sub> = 50-80 mL/min) and moderate (CL<sub>cr</sub> = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil citrate (50 mg) was not altered. In volunteers with severe (CL<sub>cr</sub> <30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in increases in AUC (100%) and C<sub>max</sub> (88%) compared to age-matched volunteers with no renal impairment.

A starting dose of 25 mg should be considered in patients with severe renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

### **Sexual Function/Reproduction**

Although **priapism** had not been reported during clinical trials, prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently during the post-marketing surveillance 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 (see **ADVERSE REACTIONS**).

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 anemia, multiple myeloma or leukemia).

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

### **Skin/Appendages**

Rare cases of Stevens-Johnson's Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported during the post-marketing period

### **Special Populations**

**Women, Nursing Mothers, Pregnancy:** Sildenafil citrate is not indicated for use in women.

**Pediatrics:** Sildenafil citrate is not indicated for use in children.

**Geriatrics (> 65 years of age):** Healthy elderly volunteers had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in younger volunteers (18 to 45 years). Since higher plasma levels may increase both the pharmacological action and incidence of some adverse events, a starting dose of 25 mg should be considered (see **ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION**).

### **Information To Patients**

Physicians should discuss with patients the increased risk of Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION) in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors. Patients should stop taking sildenafil citrate and consult their physician if they experience a decrease in, or loss of, vision in one or both eyes.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

#### **Pre-Marketing Experience:**

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

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for sildenafil citrate (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

#### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In trials of all designs, adverse events reported by patients receiving sildenafil citrate were generally similar. In fixed-dose studies, the incidence of some 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 ≥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	15.8%	3.9%
Flushing	10.5%	0.7%
Dyspepsia	6.5%	1.7%
Nasal Congestion	4.2%	1.5%
Respiratory Tract Infection	4.2%	5.4%
Flu Syndrome	3.3%	2.9%
Urinary Tract Infection	3.1%	1.5%
Abnormal Vision*	2.7%	0.4%
Diarrhea	2.6%	1.0%
Dizziness	2.2%	1.2%
Rash	2.2%	1.4%
Back Pain	2.2%	1.7%
Arthralgia	2.0%	1.5%

\* Abnormal Vision: Mild and transient changes, predominantly impairment of colour discrimination (blue/green), but also increased perception to light or blurred vision.

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

### **Less Common Clinical Trial Adverse Drug Reactions (<2%)**

The following events occurred in <2% of patients in controlled clinical trials where a causal relationship is uncertain:

***Autonomic:*** sweating, dry mouth;

***Cardiovascular:*** abnormal electrocardiogram, angina pectoris, arrhythmia, AV block, cardiac arrest, cardiomyopathy, heart failure, hypertension, hypotension, palpitation, postural hypotension, myocardial ischemia, syncope, tachycardia, varicose vein, vascular anomaly;

***Central & Peripheral Nervous System:*** tremor, abnormal dreams, anxiety, agitation, ataxia, depression, insomnia, nervousness, somnolence, paresthesia, vertigo, speech disorder, reflexes decreased, hyperesthesia, neuropathy, migraine, myasthenia, oculogyric crisis, neuralgia, hypertonia;

***Gastrointestinal:*** vomiting, gastritis, gastrointestinal disorder, flatulence, increased appetite, gastroenteritis, stomatitis, eructation, dysphagia, colitis, glossitis,



constipation, rectal hemorrhage, mouth ulceration, esophagitis, rectal disorder, gingivitis, tooth disorder;

**Hematopoietic:** anemia and leukopenia;

**Liver/Biliary:** liver function tests abnormal, ALT increased;

**Metabolic/Nutritional:** edema, thirst, gout, hyperuricemia, hypoglycemic reaction, unstable diabetes, hyperglycemia, hyperlipidemia, hyponatremia;

**Musculoskeletal:** myalgia, bone disorder, arthrosis, arthritis, tendon rupture, tenosynovitis, bone pain, joint disorder, synovitis;

**Respiratory:** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, respiratory disorder, carcinoma of lung, sputum increased, cough increased;

**Skin/Appendages:** skin carcinoma, skin disorder, skin hypertrophy, skin ulcer, contact dermatitis, exfoliative dermatitis, pruritus, urticaria, photosensitivity reaction, nail disorder, acne, herpes simplex, furunculosis;

**Special Senses:** Sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, eye pain, tinnitus, ear pain, lacrimation disorder, eye disorder, eye hemorrhage, ear disorder, cataract, dry eyes;

**Urogenital:** penile erection, other sexual dysfunction, cystitis, nocturia, balanitis, urinary frequency, breast enlargement, prostatic disorder, testis disorder, urinary incontinence, urinary tract disorder, urine abnormality, abnormal ejaculation, genital edema and anorgasmia;

**Vascular Disorders:** cerebrovascular disorder, cerebral thrombosis;

**General:** face edema, peripheral edema, chills, allergic reaction, asthenia, pain, infection, shock, hernia, accidental fall, abdominal pain, chest pain, accidental injury, intentional overdose.

In an analysis of double blind placebo controlled clinical trials encompassing over 700 person-years of observation on placebo and over 1300 person-years on sildenafil, there were no differences in the incidence rate of myocardial infarction (MI) or in the rate of cardiovascular mortality for patients receiving sildenafil compared to those receiving placebo. The rates of MI were 1.1 per 100 person-years for men receiving sildenafil and for those receiving placebo. The rates of cardiovascular mortality were 0.3 per 100 person-years for men receiving sildenafil and those receiving placebo.

### **Post-Market Adverse Drug Reactions**

Reports of adverse events temporally associated with sildenafil citrate during post-marketing surveillance that are not listed above and for which the causal relationship is unknown, include the following:

***Cardiovascular:***

Epistaxis; serious cardiovascular events - including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, and transient ischemic attack - have been reported. Most 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 with 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 combination of these factors, or to other factors (see **WARNINGS AND PRECAUTIONS**).

***Central & Peripheral***

***Nervous System:*** seizure, seizure recurrence, transient global amnesia;

***Gastrointestinal:*** vomiting;

***Urogenital:*** prolonged erection, priapism (see **WARNINGS AND PRECAUTIONS**) and hematuria;

***Skin / Appendages:*** Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

***Special Senses:*** diplopia, temporary vision loss/decreased vision, blurred vision, Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION), retinal vein occlusion, visual field defect, eye pain, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease of bleeding, vitreous detachment/traction and paramacular edema.

Cases of sudden decrease or loss of hearing have been reported post-marketing 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 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 **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and PART III CONSUMER INFORMATION**).

Rare cases of central serous chorioretinopathy have been reported during the post-marketing period in temporal association with the use of sildenafil citrate. It is not known if medical and other facts were reported that may have also played a role in the development of the condition. It is not possible to determine whether the development of the condition was related directly to the use of sildenafil, to the patient's possible underlying risk factors, a combination of these factors, or to other factors. These cases of central serous chorioretinopathy in patients receiving sildenafil did not provide evidence of serious or permanent alteration in visual function. (SEE **WARNINGS AND PRECAUTIONS**).

## DRUG INTERACTIONS

### Serious Drug Interactions

- Use of organic nitrates in any form is absolutely contraindicated (see Contraindications section)

### Overview

#### ***In vitro* studies:**

Sildenafil metabolism is principally mediated by the cytochrome P-450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route) (see **ACTION AND CLINICAL PHARMACOLOGY**). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

Sildenafil is a weak inhibitor of the cytochrome P-450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ( $IC_{50} > 150 \mu M$ ). Given sildenafil peak plasma concentrations of approximately 1  $\mu M$  after recommended doses, it is unlikely that sildenafil citrate will alter the clearance of the substrates of these isoenzymes.

#### ***In vivo* studies:**

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

### Drug-Drug Interactions

#### **Effects of Other Drugs on Sildenafil Citrate**

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, angiotensin converting enzyme (ACE) inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

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 principle circulating metabolite.

#### CYP3A4 Inhibitors

The concomitant use of potent cytochrome P-450 3A4 inhibitors (e.g. erythromycin, saquinavir, ritonavir, ketoconazole, itraconazole) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION, DETAILED PHARMACOLOGY**).

When a single 100 mg dose of sildenafil citrate 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).

When the dose of sildenafil for subjects receiving potent CYP3A4 inhibitors was administered as recommended, the maximum free plasma sildenafil concentration did not exceed 200 nM for any individual and was consistently well tolerated.

Cimetidine (800 mg), a cytochrome P450 inhibitor and a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil citrate (50 mg) to healthy volunteers.

Population pharmacokinetic 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.

#### HIV Protease Inhibitor

In addition, coadministration of the HIV protease inhibitor saquinavir, also CYP3A4 inhibitor, at steady state (1200 mg t.i.d) 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. Stronger CYP3A4 inhibitors such as ketoconazole, itraconazole would be expected to have still greater effects (see **DOSAGE AND ADMINISTRATION**).

Coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P-450 inhibitor, at steady state (500 mg b.i.d) 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 the marked effects of ritonavir on a broad range of P-450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics (see **DOSAGE AND ADMINISTRATION**).

#### CYP3A4 Inducers

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

#### CYP2C9 Substrate

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

#### Antacids

In normal healthy male volunteers, co-administration of single doses of antacid (magnesium hydroxide/aluminium hydroxide) with sildenafil did not affect the AUC,  $C_{max}$ , elimination rate constant, or subsequent half-life of sildenafil. The  $T_{max}$  was reduced by 0.42 hours.

## Effect of Sildenafil Citrate on Other Drugs

### Alpha-blockers

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, for 25 mg, 50 mg, or 100 mg 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 **WARNINGS AND PRECAUTIONS**).

Some alpha-blockers and antidepressants have reported priapism or prolonged/painful erections in their labels.

### Bleeding Time

Sildenafil citrate (50 mg) did not potentiate the increase in bleeding time, measured using a standard simplate method, caused by acetylsalicylic acid (150 mg).

### Use with Other Concomitant Therapies:

#### Antihypertensives

When sildenafil citrate (100 mg) was co-administered with amlodipine, 5 mg or 10 mg, in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic (see **ACTION AND CLINICAL PHARMACOLOGY**).

Patients on multiple antihypertensive medications were included in the pivotal clinical trials for sildenafil citrate. Analysis of the safety database was carried out after 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. The analysis showed no differences in the adverse effect profile of patients taking sildenafil citrate with and without antihypertensive medication.

A large controlled study was performed in men with erectile dysfunction and arterial hypertension who were taking combinations of diuretics, beta blockers, ACE inhibitors and calcium channel blockers. The incidence rate of all adverse events, including those possibly related to hypotensive episodes, was consistent with observations in other patient populations. Also, there was no evidence of an increased incidence rate of any adverse event in the subgroups taking 2 antihypertensive agents and 3 or more antihypertensive agents. There was no indication of additional safety risk of sildenafil use in this subject population (see **DETAILED PHARMACOLOGY**).

### **Drug-Food Interactions**

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

Sildenafil citrate can be taken with or without food. However, 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%. AUC is decreased by 11%. The patient may find that it takes longer to work if taken with a high-fat meal (see **ACTION AND CLINICAL PHARMACOLOGY**).

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

The following factors are associated with increased plasma levels (AUC) of sildenafil:

- age 65 years or over (40%)
- hepatic impairment (e.g. cirrhosis: 84%)
- severe renal impairment (e.g. creatinine clearance <30 mL/min: 100%)
- concomitant use of potent cytochrome P-450 3A4 inhibitors (e.g. erythromycin: 182%; saquinavir: 210%; ritonavir: 1000%). It can also be expected that more potent cytochrome P-450 3A4 inhibitors such as ketoconazole and itraconazole would result in increased levels of sildenafil.

(see **Recommended Dose and Dose Adjustment, ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS**).

Sildenafil citrate has been shown to potentiate the hypotensive effects of nitrates in healthy volunteers and in patients, and is therefore contraindicated in patients who are taking any type of nitrate drug therapy, or who utilize short-acting nitrate-containing medications, due to the risk of developing potentially life-threatening hypotension. The use of organic nitrates, either regularly and/or intermittently, in any form (e.g. oral, sublingual, transdermal, by inhalation) is absolutely contraindicated (see **ACTION AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS**).

### **Recommended Dose and Dosage Adjustment**

For most patients, the recommended dose of Dom-SILDENAFIL is 50 mg taken as needed. The maximum recommended dose is 100 mg. Dosage may be decreased to 25 mg if necessary.

Since higher plasma levels may increase both efficacy and the incidence of adverse events, a starting dose of 25 mg should be considered in patients, age 65 years or over, on concomitant CYP3A4 inhibitors, with severe renal impairment, with hepatic impairment and on ritonavir (see **Dosing Considerations above, ACTION AND CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS**).

The concomitant use of the potent cytochrome P-450 3A4 inhibitor, ritonavir is associated with a 1000% (11-fold) increase in plasma levels (AUC) of sildenafil. 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 **WARNINGS AND PRECAUTIONS**).

### **Administration**

To be taken as needed approximately 30 – 60 minutes before sexual activity. However, Dom-SILDENAFIL may be taken anywhere from 0.5 hour to 4 hours before sexual activity. The maximum recommended dosing frequency is once per day.

## **OVERDOSAGE**

In studies with healthy volunteers of single doses of 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. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

### **Treatment of Priapism**

Patients should be instructed to report any erections persisting for more than 4 hours to a physician. The treatment of priapism/prolonged erection should be according to established medical practice. Physicians may refer to two suggested protocols for detumescence presented below.

### **Detumescence Protocols**

- 1) Aspirate 40 to 60 mL blood from either left or right *corpora* using vacutainer and holder for drawing blood. Patient will often detumescence while aspirating. Apply ice for 20 minutes post aspiration if erection remains.

If procedure 1) is unsuccessful, then try procedure 2).

- 2) Put patient in supine position. Dilute 10 mg phenylephrine into 20 mL distilled water for injection (0.05%). With an insulin syringe, inject 0.1 to 0.2 mL (50-100 µg) into the corpora every 2 to 5 minutes, until the detumescence occurs. The occasional patient may experience transient bradycardia and hypertension when given phenylephrine injections, therefore monitor patient's blood pressure and pulse every 10 minutes. Patients at risk include those with cardiac arrhythmias and diabetes. Refer to the prescribing information for phenylephrine before use. **Do not give phenylephrine to patients on MAO inhibitors.** When phenylephrine is used within the first 12 hours of erection, the majority of patients will respond.

If procedure 2) is unsuccessful, then try procedure 3).

- 3) If the above measures fail to detumescence the patient, a urologist should be consulted as soon as possible, especially if the erection has been present for many hours. If priapism is not treated immediately, penile tissue damage and/or permanent loss of potency may result.

For management of a suspected drug overdose, contact your regional  
Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Sildenafil citrate is a cGMP-specific phosphodiesterase type 5 (PDE5) inhibitor, used for the treatment of male erectile dysfunction.

The physiological mechanism responsible for erection of the penis involves the release of nitric oxide (NO) in the *corpus cavernosum* in response to 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 has no direct relaxant effect on isolated human *corpus cavernosum*, but enhances the effect of NO by inhibiting PDE5, which is responsible for the biodegradation of cGMP in the *corpus cavernosum*. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil produces increased levels of cGMP in the *corpus cavernosum*, resulting in smooth muscle relaxation and increased inflow of blood to the *corpus cavernosum*. Sildenafil, at recommended doses, has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that sildenafil has between 10 and 10,000-fold greater selectivity for PDE5 than for other phosphodiesterase isoforms namely PDEs 1, 2, 3, 4, and 6 and greater than 700-fold effect on PDE7-PDE11. 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. Sildenafil is about 10-fold as potent for PDE5 compared to PDE6, an isoenzyme found in the retina; this lower selectivity is thought to be the basis for colour vision abnormalities observed with higher doses or plasma levels of sildenafil (see **WARNINGS AND PRECAUTIONS, DETAILED PHARMACOLOGY**).

PDE5 is also found in lower concentrations in platelets, vascular and visceral smooth muscles, and skeletal muscle. The sildenafil-induced inhibition of PDE5 in these tissues appears to be the basis for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, and inhibition of platelet thrombus formation *in vivo*, and peripheral arterial-venous dilation *in vivo* (see **WARNINGS AND PRECAUTIONS**).

### **Pharmacodynamics**

#### **Effects of Sildenafil Citrate on Blood Pressure (BP):**

Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease of 8.3/5.3 mm Hg). The decrease in blood pressure



was most notable approximately 1-2 hours after dosing. The effects are not related to dose or plasma levels. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

**Effects of Sildenafil Citrate on Cardiac Parameters:**

Single oral doses of sildenafil citrate up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG.

**Effects of Sildenafil Citrate on Erectile Response:**

Sildenafil citrate was studied in clinical trials of various designs. In fixed-dose clinical trials, 62%, 74%, and 82% of patients on 25 mg, 50 mg and 100 mg of sildenafil citrate, respectively, reported an improvement in their erections, compared to 25% on placebo ( $p < 0.0001$ , see **CLINICAL TRIALS**).

In eight double-blind, placebo-controlled, cross-over studies using RigiScan<sup>®</sup> (a device used to objectively measure penile rigidity and duration of erections), erections during sexual stimulation improved significantly on sildenafil citrate compared to placebo. These studies included patients with organic etiologies (such as spinal cord injury and diabetes mellitus), and patients without an established organic cause. Most studies assessed the efficacy of sildenafil citrate approximately 60 minutes post-dose.

All eight studies investigating the effects of sildenafil on penile plethysmography (RigiScan<sup>®</sup>) after visual sexual stimulation (VSS) under laboratory conditions, consistently showed that doses of up to 100 mg resulted in statistically significant improvements in duration of erections of 60% rigidity (considered hard enough for penetrative sexual intercourse), compared with placebo. In patients who respond, the median time to onset of erections (60% rigidity) in response to VSS, was 25 minutes after an oral dose of 50 mg sildenafil. The mean total duration of erections 60% rigidity at the base of the penis was 3, 24 and 32 minutes for subjects receiving placebo, 25 mg and 50 mg doses, respectively, when exposed to VSS for 2 hours.

Sildenafil citrate increases couples' ability to have sexual intercourse (see **CLINICAL TRIALS**).

**Pharmacokinetics**

**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 bioavailability is 41% (range 25%-63%). The oral pharmacokinetics of sildenafil citrate is proportional over the recommended dose range studied (25 mg to 100 mg).

Sildenafil inhibits the human PDE5 enzyme *in vitro* by 50% at a concentration of 3.5 nM. In man, the mean maximum free plasma concentration of sildenafil following a single oral dose of 100 mg is approximately 18 ng/mL, or 38 nM.

When sildenafil citrate was administered with a high-fat meal, the rate of absorption was significantly decreased, with a 29% reduction in  $C_{max}$  and a 60-minute delay in  $T_{max}$ . The patient may find that it takes longer to work if taken with a high-fat meal. However, although it was statistically significant (AUC decreased by 11%), the decrease in the extent of absorption was not

clinically relevant. The relative bioavailability fed/fasted was 89% (90% CI; 84-94%) (see **DRUG INTERACTIONS**).

**Distribution:** The mean steady state volume of distribution ( $V_{ss}$ ) for sildenafil is 105 litres, 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.

Based upon measurements of sildenafil in the semen of healthy volunteers, less than 0.001% of the ingested dose may appear in the semen of patients 90 minutes after drug intake.

**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 at the N-methyl piperazine moiety. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency against 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 hours.

**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 feces (approximately 80% of administered dose) and to a lesser extent in the urine (approximately 13% of the administered dose).

### **Special Populations and Conditions**

**Geriatrics:** Healthy elderly subjects (65 years or older) 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 %.

**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 (Child-Pugh class C) have not been studied.

Since sildenafil clearance is reduced in geriatric patients (65 years or older), patients with renal impairment or patients with hepatic impairment, a starting dose of 25 mg should be considered. Based on efficacy and toleration, the dose may be increased to 50 mg or 100 mg (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

**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 ( $CL_{Cr}$  <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.

In addition, N-desmethyl metabolite AUC and  $C_{max}$  values were significantly increased by 200 % and 79 % respectively in subjects with severe renal impairment compared to subjects with normal renal function.

## STORAGE AND STABILITY

Store at controlled room temperature between 15 and 30°C.

## SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dom-SILDENAFIL (sildenafil citrate)

**25 mg Tablets** (sildenafil citrate equivalent to 25 mg of sildenafil per tablet) are supplied as blue, diamond-shaped, coated tablet, debossed with “SD” and “25” on one side and plain on the other side and supplied as follows:

- Dom-SILDENAFIL Tablets are packaged in HDPE bottles of 30 tablets.
- Dom-SILDENAFIL Tablets are packaged in Blister packs of 4 tablets.

**50 mg Tablets** (sildenafil citrate equivalent to 50 mg of sildenafil per tablet) are supplied as blue, diamond-shaped, coated tablet, debossed with “SD” and “50” on one side and plain on the other side and supplied as follows:

- Dom-SILDENAFIL Tablets are packaged in HDPE bottles of 30 tablets.
- Dom-SILDENAFIL Tablets are packaged in Blister packs of 4 and 8 tablets.

**100 mg Tablets** (sildenafil citrate equivalent to 100 mg of sildenafil per tablet) are supplied as blue, diamond-shaped, coated tablet, debossed with “SD” and “100” on one side and plain on the other side and supplied as follows:

- Dom-SILDENAFIL Tablets are packaged in HDPE bottles of 30 tablets.
- Dom-SILDENAFIL Tablets are packaged in Blister packs of 4 and 8 tablets.

### Composition:

Dom-SILDENAFIL 25 mg, 50 mg & 100 mg Tablets contain 25 mg, 50 mg & 100 mg sildenafil as sildenafil citrate, respectively. The tablets contain the following non-medicinal ingredients (alphabetically): colloidal silicon dioxide, corn starch, FD&C Blue No.2 Aluminum Lake, hydroxypropyl methylcellulose, hypromellose, lactose, macrogol, magnesium stearate, polyethylene glycol, povidone, sodium lauryl sulphate, sodium starch glycolate, titanium dioxide

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

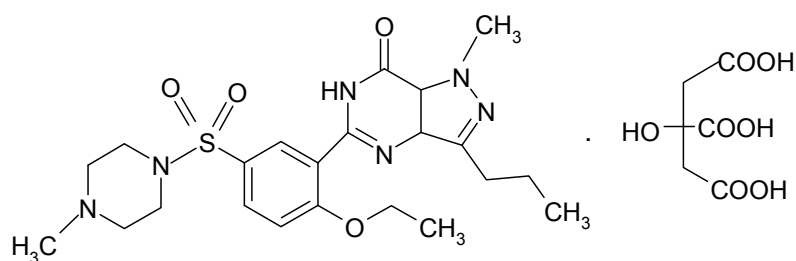
Proper name: sildenafil citrate

Chemical name:

Piperazine, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methyl-, 2-hydroxy-1,2,3- propanetricarboxylate

Molecular formula and molecular mass:  $C_{22}H_{30}N_6O_4S \cdot C_6H_8O_7$ ; 666.71 g/mol

Structural formula:



Physicochemical properties: Sildenafil citrate is a white to off-white crystalline powder.

pK <sub>a</sub> :	protonation of tertiary amine	6.53
	deprotonation of pyrimidirone moiety	9.17
Partition coefficient:	octanol / water	2.7
Solubility (23 °C):	water	3.5 mg/mL
	1M HCl	5.8 mg/mL
	1M NaOH	42.3 mg/mL

## CLINICAL TRIALS

### Comparative Bioavailability Studies

A blind, randomized, two-way crossover bioequivalence study was performed in normal healthy male volunteers (n=26) under fasting conditions on sildenafil tablets using Dominion Pharmacal. Dom-SILDENAFIL 100 mg tablets versus the reference product, VIAGRA<sup>®</sup> 100 mg Tablets, by Pfizer Canada Inc. The pharmacokinetic data calculated for the Dom-SILDENAFIL 100 mg tablets and VIAGRA<sup>®</sup> 100 mg tablets formulations are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Sildenafil (1 x 100 mg tablet, fasted) From measured data <b>uncorrected for potency</b> Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference <sup>†</sup>	% Ratio of Geometric Means	Confidence Interval 90%
AUC <sub>T</sub> (ng·h/mL)	1267.67 1369.25 (40.41)	1291.07 1372.50 (36.43)	98.19	91.21 – 105.69
AUC <sub>I</sub> (ng·h/mL)	1301.71 1405.50 (40.35)	1335.94 1417.98 (36.89)	97.44	90.77 – 104.60
C <sub>max</sub> (ng/mL)	382.56 421.25 (48.21)	404.30 446.82 (51.88)	94.62	81.02 – 110.51
T <sub>max</sub> <sup>§</sup> (h)	1.00 (0.500 – 4.00)	0.759 (0.500 – 2.50)		
T <sub>1/2</sub> <sup>  </sup> (h)	3.13 (34.92)	3.62 (44.50)		

\* Dom-SILDENAFIL (Sildenafil citrate) 100 mg Tablets, Dominion Pharmacal, Montreal, Canada

<sup>†</sup> VIAGRA<sup>®</sup> (Sildenafil Citrate) 100 mg Tablets, Pfizer Canada Inc. are purchased in Canada.

<sup>§</sup> Expressed as the median (range)

<sup>||</sup> Expressed as the arithmetic mean (CV%)

### Study demographics and trial design

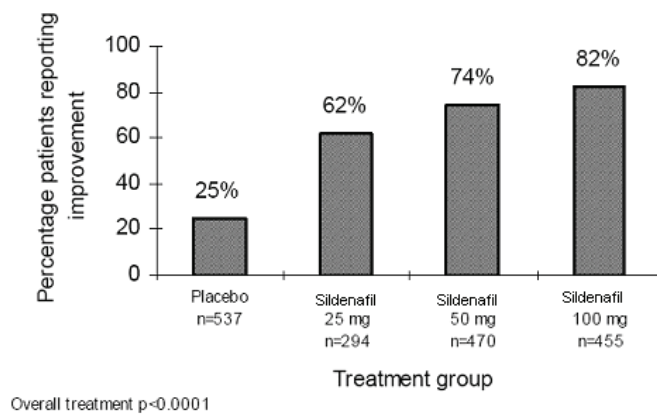
Sildenafil citrate was evaluated at doses including 25 mg, 50 mg and 100 mg in 21 randomized, double-blind, placebo-controlled trials of up to 6 months duration. In these studies, sildenafil citrate was administered to more than 3000 patients aged 19 to 87 years, with ED of various etiologies (organic, psychogenic, mixed) with a mean duration of 5 years.

This patient population included men with the following concomitant conditions: angina, benign prostatic hyperplasia (BPH), depression, type I and type II diabetes mellitus, hypertension, previous myocardial infarction, radical prostatectomy, spinal cord injury, transurethral resection of the prostate (TURP), and vasculogenic disease.

Efficacy was demonstrated in all 21 studies and results were consistent regardless of baseline severity, etiology and age. Efficacy was maintained over the long-term (1 year). Sildenafil citrate was effective in a broad range of ED patients, including those with a history of coronary artery disease (myocardial infarction, angina), hypertension, other cardiac disease (arrhythmias, congestive heart failure), peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass graft (CABG), radical prostatectomy and TURP, and in patients taking antidepressants, antihypertensives, antipsychotics, and diuretics.

### Study results

Sildenafil citrate was studied in clinical trials of various designs. In fixed-dose clinical trials, 62%, 74%, and 82% of patients on 25 mg, 50 mg and 100 mg of sildenafil citrate, respectively, reported an improvement in their erections, compared to 25% on placebo (see **Figure 1**).



**Figure 1** - Percentage of Patients reporting an Improvement in Erections

The primary efficacy endpoints were the ability to both achieve and maintain an erection sufficient for sexual intercourse, as measured by patient responses to the International Index of Erectile Function (IIEF), a sexual function questionnaire. The results from the partner questionnaire corroborated the data from the study subjects, with analyses showing clear treatment related improvements in the ability to achieve and maintain erections.

Responses to the IIEF are scored on a five-point scale ranging from ‘almost never/never’ (1) to ‘almost always/always’ (5), with a score of (0) assigned for no attempts at sexual intercourse. During IIEF validation, scores for the primary efficacy endpoints for men without erectile dysfunction were 4.38 and 4.34, respectively. Compared to baseline treatment over 12 weeks, sildenafil citrate patients reported the following statistically significant changes (see **Figure 2**).

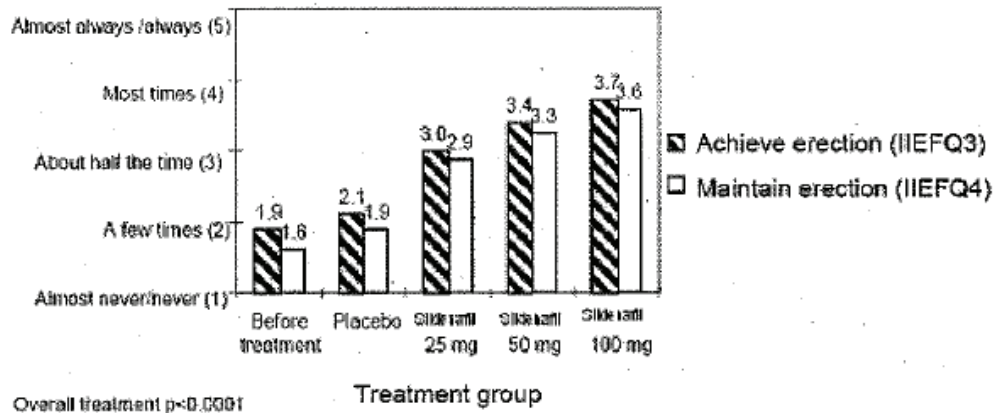


Figure 2 - Effect of Sildenafil Citrate on Ability to Achieve and Maintain an Erection Sufficient for Sexual Intercourse

Men with untreated ED have lower scores (Figure 3, Bar 1) for all sexual function domains of the IIEF (erection, orgasm, desire, overall satisfaction, intercourse satisfaction). In these men, sildenafil citrate restores the values of the domains (Figure 3, Bar 2) towards the values of age matched controls without ED (Figure 3, Bar 3).

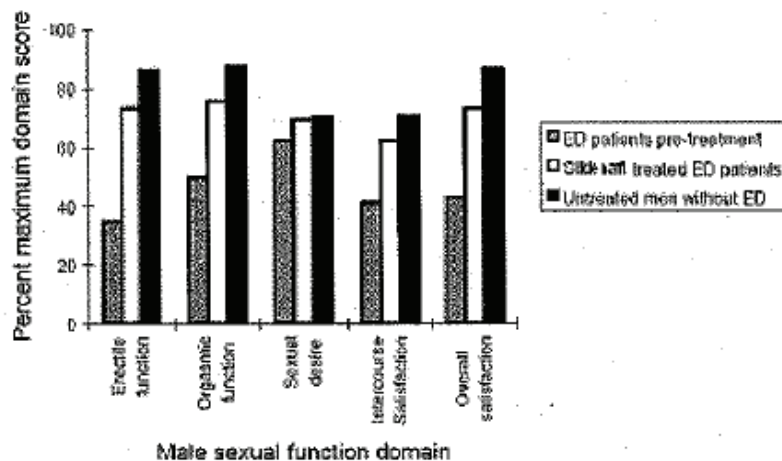


Figure 3 - Effect of Sildenafil Citrate on Male Sexual Function Domains of the IIEF

Sildenafil citrate increases couples' ability to have sexual intercourse. With sildenafil citrate, 64%, 67% and 72% of attempts resulted in successful sexual intercourse on doses of 25 mg, 50 mg, and 100 mg, respectively, compared to 23% on placebo. Of sildenafil citrate patients with one or more successful attempt at intercourse, 81% of attempts were successful.

The efficacy of sildenafil citrate was maintained over time. In a long-term, open-label trial of 12-month duration, 88% (256/292) of patients reported that sildenafil citrate treatment improved their erections. Eighty-seven percent (87%) of patients completed the one-year study. When these patients were followed for an additional year (total exposure of 24-months), oral sildenafil was an

effective, well tolerated treatment for erectile dysfunction of organic, psychogenic or mixed aetiology.

In a controlled clinical study which reflects the recommended dosage regimen, 74% of patients were taking sildenafil citrate 100 mg after 12 weeks of treatment, compared to 23% and 3% taking sildenafil citrate 50 mg and 25 mg, respectively.

### **Other Patient Populations:**

Across all trials, sildenafil citrate improved the erections of 59% of diabetic patients, and 43% of radical prostatectomy patients (versus 16% and 15% on placebo, respectively). This was assessed using the GAQ.

In a study of patients with spinal cord injury, sildenafil citrate improved the ability to have sexual intercourse in 80% of patients versus 10% on placebo.

Subgroup analyses of responses to a global improvement question in patients with psychogenic etiology in two fixed-dose studies and two titrations studies showed 84% of sildenafil citrate patients reported improvement in erections compared with 26% of placebo patients.

These studies confirm that sildenafil enhances the erectile response to sexual stimulation in subjects with erectile dysfunction (ED) of psychogenic and broad-spectrum etiology, including patients with diabetes mellitus and with spinal cord injury.

### **Use with Other Concomitant Therapies:**

#### **Antihypertensives**

A large (n=568) randomized, double-blind, placebo-controlled, parallel group, multicenter, flexible-dose study (sildenafil citrate up to 100 mg) in males with erectile dysfunction and arterial hypertension taking 2 or more antihypertensive agents was conducted (the majority of these were diuretics, beta blockers, ACE inhibitors and calcium channel blockers). Fifty-eight percent of the patients were taking 2 antihypertensive agents and 42% were taking 3 or more antihypertensive agents composed of similar groups of drugs for blood pressure control. Sildenafil citrate improved the erections in 71% of men compared to 18% in the placebo group, and 62% of attempts at sexual intercourse were successful with sildenafil citrate compared to 26% on placebo. The incidence rate of all adverse events, including those possibly related to hypotensive episodes, was consistent with observations in other patient populations. Also, there was no evidence of an increased incidence rate of any adverse event in the subgroups taking 2 antihypertensive agents and 3 or more antihypertensive agents. There was no indication of additional safety risk of sildenafil use in this subject population (see **WARNINGS AND PRECAUTIONS**).



## DETAILED PHARMACOLOGY

### Human

#### **Pharmacodynamic Studies**

Oral doses of sildenafil of 50 mg, 100 mg and 200 mg produced statistically significant decreases in supine systolic and diastolic blood pressure (a mean maximum decrease of approximately 8 mm Hg and 5 mm Hg, respectively) compared with placebo, with no effect on pulse rate. The mean maximum fall in systolic and diastolic blood pressure occurred at peak plasma levels (approximately 1 hour post-dose), and there was a tendency for blood pressure to return to baseline values by 4 hours post-dose.

In healthy volunteers, there were no clinically significant changes in cardiac index (derived from bio-impedance measures of cardiac output) up to 12 hours post-dose for sildenafil administered orally (100 mg, 150 mg and 200 mg), nor intravenously (20-80 mg), compared with placebo. Sildenafil has both arteriodilator and venodilator effects on the peripheral vasculature.

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 had no effect on cardiac output, and did not impair blood flow through the stenosed coronary arteries, and resulted in improvement (approximately 13%) in adenosine-induced coronary flow reserve (in both stenosed and reference arteries).

In a double-blind study, 144 patients with erectile dysfunction and chronic stable angina limited by exercise, not receiving chronic oral nitrates, were randomized to a single dose of placebo or sildenafil citrate 100 mg 1 hour prior to exercise testing. The primary endpoint was time to limiting angina in the evaluable cohort. The mean times (adjusted for baseline) to onset of limiting angina were 423.6 and 403.7 seconds for sildenafil (N=70) and placebo, respectively. These results demonstrated that the effect of sildenafil citrate on the primary endpoint was statistically non-inferior to placebo. It should be noted that the results presented were from a controlled clinical research trial in which selected patients were carefully screened and monitored.

After patients have taken sildenafil citrate, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post-dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL). In the following patients: age >65, hepatic impairment (e.g. cirrhosis), severe renal impairment (e.g. creatine clearance <30 mL/min), and concomitant use of potent cytochrome P-450 3A4 inhibitors (erythromycin), plasma levels of sildenafil at 24 hours post-dose have been found to be 3 to 8 times higher than those seen in healthy volunteers. Although plasma levels of sildenafil at 24 hours post-dose are much lower than at peak concentration, it is unknown whether nitrates can be safely coadministered at this time point (see **CONTRAINDICATIONS**).

Single oral doses of sildenafil above 15 mg were generally associated with a potentiation of the antiaggregatory effects of sodium nitroprusside (SNP) on ADP aggregation of *ex vivo* platelets. Sildenafil had no effect on other *ex vivo* tests (ADP-induced platelet aggregation of whole blood and ADP-induced aggregation of platelet-rich plasma in the absence of SNP). Sildenafil therefore has no direct effect on platelet function *ex vivo*, but potentiates the action of a nitric oxide (NO) donor, SNP. This confirms the need for an NO drive before sildenafil will produce its pharmacological effects. These modest effects on platelet activity, *ex vivo*, did not result in a clinically significant effect on bleeding time in healthy volunteers.

#### **Effect of Sildenafil Citrate on Sperm Motility:**

Sildenafil had no effect on sperm motility, morphology, count, density, vitality, ejaculate volume or viscosity. The concentrations of sildenafil in the ejaculate, 1.5 hours and 4 hours post-dose, were 18% and 17%, respectively, of the concentrations in plasma at the same time points. The concentrations of the metabolite, at the same time points were 5% and 15%, respectively.

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

#### **Effects of Sildenafil Citrate on Vision:**

At single oral doses of 100 mg and 200 mg, transient dose-related impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of sildenafil citrate on visual acuity, contrast sensitivity, ERGs, intraocular pressure, or pupillometry. In flexible titration studies of 4 to 26 weeks, 3% of patients on sildenafil reported visual disturbances: mild and transient impairment of colour discrimination (predominantly blue/green), and also increased perception to light or blurred vision (see **WARNINGS AND PRECAUTIONS**).

In healthy volunteers aged 40-65 years, single doses of sildenafil up to 200 mg had no clinically relevant effect on visual acuity, contrast sensitivity, pupil diameter and constriction velocity, visual fields, recovery time following dazzle, electroretinogram or intraocular pressure. Modest, transient changes in colour discrimination were observed (Farnsworth-Munsell 100 Hue test) after 100 mg and 200 mg doses, but not at 50 mg. At 100 mg, this effect was apparent only at one hour after dose and at 200 mg, up to two hours after dose.

In a placebo-controlled, crossover study of patients with documented early age-related macular degeneration (n=9), sildenafil (single dose, 100mg) was well-tolerated and demonstrated no clinically significant changes in the visual tests conducted (visual acuity, Amsler grid, color discrimination, simulated traffic light, Humphrey perimeter and photostress).

#### **Pharmacokinetic Studies**

When administered orally to healthy male volunteers in the fasted state, sildenafil was rapidly absorbed, with maximum observed plasma concentrations ( $C_{max}$ ) occurring 0.5-2 hours after dosing in most subjects.  $C_{max}$  and areas under the plasma concentration time curve to infinite time (AUC) increased in a proportional manner with dose over the clinical dose range 25-100 mg.

Sildenafil has an apparent volume of distribution at steady state ( $V_{ss}$ ) of 105 litres and a mean plasma clearance (CL) of 41 L/h. Both  $V_{ss}$  and CL were shown to be significantly correlated to body weight. The absolute oral bioavailability was 41%. Sildenafil has a terminal half-life of approximately 4 hours (range 2-8 hours). Approximately 96% of sildenafil is bound to plasma proteins.

### **Metabolism and Elimination**

The major circulating metabolite of sildenafil, results from N-demethylation of sildenafil at the N-methyl piperazine moiety. It has a similar selectivity for PDE isozymes as sildenafil, but exhibits around 50% of the potency of sildenafil. The metabolism of sildenafil occurs in human hepatic microsomes and is mediated by two cytochrome P-450 isoforms [CYP2C9 (minor route) and CYP3A4 (major route)].

The concomitant use of potent cytochrome P-450 3A4 inhibitors (e.g. erythromycin, saquinavir, ritonavir, ketoconazole, itraconazole) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

## TOXICOLOGY

### Acute Toxicity Mice and Rats:

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>Single dose oral toxicity in mice and rats (90155/56)</b>					
Sprague-Dawley rat CD1 mice	Oral (gavage)	rat: 300 500 1000 mice: 500 1000	5/sex	1 day	<p>At 1000 mg/kg one male mouse died within 24 hours after drug administration. In rats, mortality occurred in three females at 1000 mg/kg and in one female at 500 mg/kg. The dose of 1000 mg/kg induced clinical signs in both species, generally within 24 hours following the administration, which persisted less than 24-48 hours. Some of these signs were similar in mice and rats and consisted of partially-closed eyes, hunched posture, tremours, depression, coldness to the touch (with pallor of ears and paws in rats) and prostration. Female rats were more affected than male rats. Dyspnea was limited to one mouse, and chromodacryorrhea to four female rats. Clinical signs at 500 mg/kg included partially-closed eyes in one mouse and subdued behaviour in the female rat which died. No clinical signs were observed in rats at 300 mg/kg. In both species, the doses administered induced no changes in body weight gain and there were no treatment-related macroscopical changes at gross necropsy.</p> <p>These results indicate that the no observed adverse effect level (NOAEL) was 500 mg/kg in mice and 300 mg/kg in rats.</p>
<b>Single dose intravenous toxicity in mice and rats (91045/046)</b>					
Sprague-Dawley rat CD1 mice	I.V.	rat: 10 mice: 20	5/sex	1 day	<p>All animals survived the treatment and gained weight over the 14-day study period. There were no clinical signs during the study and no abnormalities at necropsy. Under the conditions of this study, the no observed effect level (NOEL) after intravenous administration was 20 mg/kg in mice and 10 mg/kg in rats.</p>

### Long-Term Toxicity - Mice:

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>3-Month oral (gavage) prechronic toxicity study in mice (94049)</b>					
CD1	Oral (gavage)	10 50 100 200	10/sex	3 months	<p>The exposure to sildenafil and its metabolite UK-103,320 was similar in males and females and approximately dose-related. Treatment-related mortality occurred in 3/20 animals in each group given 50, 100 or 200 mg/kg. A marked gastrointestinal dilation was the cause of the death and was associated with a number of clinical signs, in particular dyspnea and/or swollen abdomen. This dilation resulted in gastrointestinal inflammation, fatty changes and focal/multifocal necrosis in the liver, atrophy of adipose tissues and hemoconcentration. There was also a mild gastrointestinal dilation in a few survivors of these groups. In males treated with 50, 100 or 200 mg/kg, there was an apparent decrease in body weight gain. However, in the absence of dose relationship and consistent statistical significance, the association with treatment is questionable. Plasma cholesterol was slightly increased in females treated with 50, 100 or 200 mg/kg and plasma triglycerides were slightly decreased in males treated with 100 or 200 mg/kg. However we consider these changes to be of minor toxicological importance.</p> <p>The NOAEL in this study was 10 mg/kg, given the mortality and gastrointestinal dilation at higher doses.</p>

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>3-Month oral (gavage) exploratory toxicity study in mice (94101)</b>					
CD1	Oral (gavage)	20 40 100	10/sex	3 months	<p>The exposure to sildenafil and its metabolite UK-103,320 was similar in males and females and increased superproportionally with dose level. Treatment-related mortality occurred in 1/20 animals in each group given 40 or 100 mg/kg. A marked gastrointestinal dilation was the cause of the death and was associated with a number of clinical signs, in particular dyspnea and/or swollen abdomen. There was also a transient abdominal swelling in a few survivors of these groups.</p> <p>The NOAEL in this study was 20 mg/kg, given the mortality and gastrointestinal dilation at higher doses.</p>

### Long-Term Toxicity - Rats:

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>10-Day oral range-finding toxicity in rats (90080)</b>					
Sprague Dawley	Oral (gavage)	50 150 500	5/sex	10 days	<p>Measurement of plasma concentrations of sildenafil and UK-103,320 showed that females were exposed predominantly to the drug while males were exposed mainly to the metabolite, UK-103,320, and a lower level of unchanged compound. Concentrations of UK-95,340 were generally below the limit of determination (30 ng/mL). Exposure increased with dose but not in linear manner. At 500 mg/kg, 1/5 females died after the second dose with no apparent cause of death. Of the animals used for plasma drug determination, 1/10 rats at 150 mg/kg and 2/10 rats at 500 mg/kg died after the first or second dose. As these animals died after taking blood samples, they were not considered in the analysis of mortality. Food consumption was decreased between day 1 and 4 in mid- and high-dose males and in all treated female groups. A dose-related decrease of plasma triglycerides occurred in males, and an increase of plasma cholesterol was seen in high-dose females. Blood urea increased in mid- and high-dose males and in the 3 treated female groups. Relative heart weight was slightly increased in high-dose males. Kidney and liver weights were increased in mid- and high-dose females, and in high-dose males. The increase of liver weight was associated with centrilobular hypertrophy. Changes in red blood cell parameters were seen in females. They indicate a decrease of circulating red blood cells at the 3 dose levels, with some evidence of regenerative response at the high dose. An increase of white blood cell counts was recorded at the mid dose in females and at the high dose in both sexes. Changes at the dose of 50 mg/kg were considered minor.</p> <p>The NOAEL in this study was 150 mg/kg, based on the mortality at 500 mg/kg.</p>
<b>1-Month oral toxicity in rats (90143)</b>					
Sprague Dawley	Oral (gavage)	10 45 200	10/sex	1 month	<p>Plasma concentrations of sildenafil were higher in females than in males, while concentrations of the metabolite, UK-103,320, were higher in males than in females. As a result, females were exposed predominantly to the unchanged drug and males to an almost equal balance of drug and metabolite. These data indicate that N-demethylation of sildenafil to UK-103,320 is an important route of sildenafil biotransformation in male rats. Concentrations of UK-95,340 were generally below the limit of determination (30 ng/mL).</p> <p>One of the high-dose females used for plasma drug level determination died after the first dose, before blood samples had been taken. Clinical signs were limited to a few high-dose animals and consisted of chromodacryorrhea and palpebral closure. Slight increases in water and food intake were seen generally in mid- and high-dose animals. A mild dose-related decrease in circulating red blood cells with evidence of a regenerative response was found in mid- and high-dose females and, to a smaller extent, in high-dose males. A moderate neutrophilia was seen in high-dose males, while a moderate lymphocytosis occurred in mid- and high-dose females. Plasma chemistry changes at the high dose consisted of increases in urea, decreases in triglycerides (males) and increases in cholesterol (females), but remained within our normal range of values. Doses of 45 and/or 200 mg/kg were associated with an increase in liver weight and</p>

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
					centrilobular hypertrophy in both sexes. Hypertrophy of the zona glomerulosa of the adrenal glands was seen in the high-dose males and in the mid- and high-dose females. Thyroid follicular hypertrophy occurred at the high dose in both sexes. In addition, mesenteric arteritis was found in two mid-dose and one high-dose males, but was not considered to be related to the treatment. The NOAEL was 45 mg/kg in this study.
<b>28-Day oral exploratory toxicity study in rats (94085)</b>					
Sprague-Dawley	Oral (gavage)	0 60 120	10 males/ group	28 days	<p>A 2-year rat carcinogenicity study with sildenafil citrate at a contract laboratory (Study No. 911/002), at doses of 1.5, 5 and 60 mg/kg, was terminated after unexpectedly high mortality and severe toxic effects in high-dose males during weeks 3 and 4. An exploratory study was performed to confirm that the batch of sildenafil used at the contract laboratory did not induce severe toxicity.</p> <p>The only treatment-related effects were a mild dose-related increase in liver and kidney weights and possibly a slight decrease in body weight gain. Importantly, the absence of death in this study confirms the results of previous studies up to 200 mg/kg, and contrasts with the results of the study at the contract laboratory. Subsequently, it was shown that the mortality in the carcinogenicity study (Study No. 911/002) was due to dosing with a cytotoxic compound from another company and not sildenafil. Consequently, the contracted carcinogenicity study was invalid.</p>
<b>Investigation of the relationship between liver enzyme induction and thyroxine clearance in rats (96010)</b>					
Sprague-Dawley	Oral (gavage)	200	10 females	1 month	<p>Following the appearance of thyroid follicular hypertrophy in rats, an investigative study was conducted to examine the relationship between liver enzyme induction and thyroid hypertrophy in rats. Two groups of 10 female rats were treated orally with sildenafil citrate at 200 mg/kg for 29 days, and two control groups received the vehicle alone. One treated group and one control group were used for assessment of exogenous thyroxine clearance. The other treated group and the other control group were used for measurement of plasma TSH and thyroid hormones, for histopathological examination of the liver and thyroid, and for determination of UDP-glucuronyl transferase (UDPGT) activity in the liver.</p> <p>The treatment caused the deaths of 2/20 rats on days 2 or 3. In the treated group, there was an increase in the weight of liver and thyroid, associated with minimal centrilobular hypertrophy of the liver and thyroid follicular cell hypertrophy. There was also an increase in hepatic UDPGT activity, an increase in TSH, and a decrease in T3 and T4 hormones. In addition, the clearance of exogenous thyroxine was increased in treated animals.</p> <p>These results are consistent with the view that the thyroid hypertrophy associated with treatment of rats with sildenafil was due to induction of hepatic UDPGT which increased the clearance of thyroid hormone and consequently caused a compensatory increase in plasma TSH which stimulated the thyroid gland.</p>
<b>6-Month oral toxicity study in rats (91098)</b>					
Sprague-Dawley	Oral (gavage)	3 12 60	20/sex	6 months	<p>Drug and metabolite plasma level determinations showed that females were exposed predominantly to sildenafil while males were exposed almost exclusively to the metabolite. No treatment-related deaths were recorded. Chromodacryorrhea was seen in the 3 treated groups. Body weight gain and food consumption were increased at the low dose and, to a lesser extent, at the mid dose. A trend towards a reduced body weight gain was seen at the high dose; however, the relationship to compound administration cannot be ascertained. Decreases of plasma bilirubin and triglycerides, and increases in plasma urea, total proteins and cholesterol were seen at the high dose. These changes suggest compound-induced metabolic changes in the liver. Increase in liver weight associated with mild centrilobular hypertrophy indicate an adaptive response. Thyroid hypertrophy occurred at the high dose in both sexes and at a lower incidence in mid-dose males. This change was considered to be a secondary phenomenon related to increased hepatic clearance of thyroid hormone. Although thyroid hormones and hepatic clearance were not measured in this study, changes in these parameters were demonstrated in an exploratory study (Study No. 96010). Hypertrophy of the zona glomerulosa of the adrenal gland occurred with a dose-related incidence at the mid and high doses and was associated with an increase in the weight of the organ at 60 mg/kg.</p> <p>The NOAEL in this study was 60 mg/kg.</p>
<b>13-Day intravenous range-finding in rats (90139)</b>					
Sprague-Dawley	I.V.	2.5 5	5/sex	13 days	No deaths occurred during the treatment period. The only clinical sign noted was a transient redness of the ears in a few treated animals, notably in the high-dose

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
		10			male group. The NOAEL in this study was 10 mg/kg.
<b>1-Month intravenous toxicity study in rats (91044)</b>					
Sprague-Dawley	I.V.	0.5 2 4	10/sex	1 month	No compound-related changes were seen at the doses of 0.5 and 2 mg/kg. At the dose of 4 mg/kg, the incidence and severity of mild myocardial inflammation was slightly increased compared to the control group; the relationship to treatment cannot be ascertained. The NOAEL in this study was 2 mg/kg.

**Long-Term Toxicity - Dogs:**

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>10-Day oral range-finding toxicity in dogs (90081)</b>					
Beagle	Oral (gavage)	10 30 100	1 male 2 females	10 days	Plasma concentrations of sildenafil and UK-103,320 were similar in males and females and increased with dose, although subproportionally at the high dose. The proportion of UK-103,320 relative to sildenafil varied minimally (18-24%) over the dose range examined and indicates no detectable saturation of this metabolic pathway. Concentrations of UK-95,340 were generally below the limit of determination (30 ng/mL). Emesis and salivation occurred at the dose of 100 mg/kg, and lacrimation, conjunctival redness and a transient decrease in amplitude of the pupillary reflex were seen at all dose levels. There was no evidence of a convincing change in blood pressure, given the spontaneous variation in this parameter. Heart rate was increased at 30 and 100 mg/kg, and probably represents a reflex response to the vasodilating properties of the compound. Decreases in PQ and QT intervals of the ECG at these doses were secondary to the heart rate changes. Two high-dose animals showed a moderate increase of plasma cholesterol which was not considered to be toxicologically important. An arteritis of an extramural branch of a coronary artery was found in one high-dose female. This is considered to be a spontaneous finding considering the morphological features and the background incidence in Beagle dogs in our laboratories. The NOAEL in this study was therefore 100 mg/kg.
<b>1-Month oral toxicity study in dogs (90125)</b>					
Beagle	Oral (gavage)	5 20 80	3/sex	1 month	The dogs were exposed to concentrations of sildenafil and UK-103,320, which increased with dose, although subproportionally at the high dose. The proportion of UK-103,320 relative to sildenafil varied minimally (15-19%) over the dose range examined and indicates no detectable saturation of this metabolic pathway. Concentrations of UK-95,340 were generally below the limit of determination (30 ng/mL). At the mid and high doses, the compound induced a low incidence of emesis and transient salivation. A moderate incidence of soft and liquid feces was noted at all doses. There was no evidence of consistent changes in blood pressure, although there were increases in heart rate at 20 and 80 mg/kg. Changes in the ECG (increased P-wave amplitude and decreases in PQ and QT intervals) were expected from the increases in heart rate. There was a moderate increase in plasma cholesterol at the high dose. A mild coronary arteritis was seen in one high-dose animal, but considering the morphological features of this finding, and the high background incidence in Beagle dogs in our laboratories, this was not thought to be treatment-related. The NOAEL was 80 mg/kg in this study.

Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>6-Month oral toxicity in dogs (91099)</b>					
Beagle	Oral (gavage)	3 15 50	4/sex	6 months	Analyses of plasma sildenafil and UK-103,320 showed dose-related concentrations in the dog. The proportion of UK-103,320 relative to sildenafil varied minimally (15-23%) as the dose increased, indicating no saturation of this process. Salivation, emesis and resistance to compound administration were seen when the animals were treated with an initial high dose of 80 mg/kg, and reflected gastric intolerance to the compound at this dose level. These signs were rare after reducing the high dose to 50 mg/kg. A moderate increase in heart rate, associated with decreases in PQ and QT intervals, occurred at the high dose and is considered to be a reflex response to the vasodilatory properties of the drug. Increases in plasma cholesterol and in liver weight were seen in animals treated with 15 and 50 mg/kg. A high-dose male showed a number of clinical signs and changes in hematological parameters and plasma chemistry associated with a disseminated arteritis. These changes correspond to Idiopathic Juvenile Arteritis Syndrome (Beagle Pain Syndrome) which occurs sporadically in Beagle dogs. Another high-dose male showed arteritis in the thymus which indicated a less severe expression of the same disease. It is probable that the high dose precipitated the expression of this latent spontaneous disorder. The NOAEL in this study was 15 mg/kg, given the appearance of Idiopathic Juvenile Arteritis Syndrome at higher doses.
<b>12-Month oral toxicity study in dogs (95039)</b>					
Beagle	Oral (gavage)	3 10 50	4/sex	12 months	The dogs were exposed to approximately dose-related concentrations of sildenafil and its N-demethylated metabolite, UK-103,320. The proportion of UK-103,320 relative to sildenafil varied minimally as the dose increased. Features typical of a syndrome of Idiopathic Juvenile Arteritis occurred in all high-dose males. In 3/4 high-dose males, there was arteritis which affected several organs. In one of these dogs, arteritis was associated with a number of clinical signs, body weight loss and hematological changes. In the other two animals, there were no clinical or hematological correlates to arteritis. In addition, the fourth high-dose male presented clinical signs and clinical pathology changes typical of the syndrome though no vascular lesion was found at histopathology. Focal coronary arteritis occurred in one low-dose and one high-dose female; neither finding was considered treatment-related. The treatment produced an increase in the amount of lipogenic pigments in renal tubular epithelium in 1/8 animals at the mid dose and 7/8 animals at the high dose, a dose-related decrease in plasma creatine kinase, mainly in males, and a decrease in plasma myosin in high-dose animals. However, these changes were considered of no toxicological importance. A dose-related increase in heart rate occurred at the high and mid doses, and was considered to be due to compensatory mechanisms occurring in response to the vasodilatory properties of the compound.  The NOAEL in this study was 10 mg/kg, given the appearance of Idiopathic Juvenile Arteritis Syndrome at higher doses.
<b>14-Day intravenous range-finding toxicity in dogs (90142)</b>					
Beagle	I.V.	2.5 5 10	2 males 1 female	14 days	The doses of 5 and 10 mg/kg were associated with liquid feces and an inhibition of the pupillary reflex. An increase in heart rate was observed at the high dose and, to a lesser extent, at the mid dose. This change was probably related to the vasodilator effect of the compound. Evidence of vasodilatation was provided by the peripheral redness seen in two high-dose animals. An increase in plasma cholesterol occurred in 2/3 high-dose animals but was not considered to be toxicologically important. At the dose of 2.5 mg/kg, there were no treatment-related changes. The NOAEL was 10 mg/kg in this study.



Species	Route	Dose mg/kg/day	#Animals / dose level	Duration	Findings
<b>1-Month intravenous toxicity in dogs (91041)</b>					
Beagle	I.V.	0 0.5 2 4	3/sex	1 month	The treatment induced no adverse effects. The NOAEL is therefore 4 mg/kg in this study.

### **Bioequivalence - Dogs:**

Species	Route	Dose mg/kg / day	#Animals / dose level	Duration	Findings
<b>Bioequivalence between base and citrate in dogs (91058)</b>					
Beagle	Oral	300	1 male 1 female	N/A	<p>The aim of the current study was to assess, in the dog, the oral bioequivalence of a suspension of the base, and of capsules of the citrate. The base was suspended in a 5% aqueous solution of methylcellulose 4000 cps containing 0.1% Tween 80 and acidified with hydrochloric acid 0.1M (final concentration). The citrate salt was administered in gelatin capsules.</p> <p>On day 1, a first group of one male and one female beagle dogs was treated with the base and the second group of one male and one female was treated with the citrate. On day 8, the first group received the citrate, and the second group the base. The animals were regularly examined for clinical signs and weighed before each administration. Blood was sampled 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11 and 24 hours after each administration. Plasma levels of UK-92,480 and two metabolites, UK-95-340 and UK-103,320, were measured.</p> <p>One male dog vomited after each administration and its drug and metabolite plasma concentrations were therefore considered not to be relevant. In other dogs, maximal plasma concentrations and AUCs of UK-92,480 and of UK-103,320, observed after administration of the citrate in capsules were similar to or higher than those seen after administration of the base in a suspension. All the plasma concentration of UK-95,340 were below the limit of detection of the assay. These data indicate that bioavailability of the citrate in the dog is identical to or better than that of the base.</p>

### **Carcinogenesis and Mutagenesis**

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in systemic drug exposure (AUC) of 110- and 146-times, respectively, for male (unbound sildenafil and its major metabolite) and female (unbound sildenafil) rats. The exposures observed in humans given the Recommended Human Dose (RHD) of 20 mg t.i.d. sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 1.1 times the RHD on a mg/m<sup>2</sup> basis.

Sildenafil has been studied in a comprehensive battery of tests designed to detect genotoxic activity. Sildenafil did not display mutagenic activity in bacterial or mammalian cells *in vitro*, or clastogenic activity *in vitro* or *in vivo*.

As the clinical dose is administered three times daily, the clinical free AUC used to calculate exposure multiples was 19 ng-h/mx<sup>3</sup>, and compared with the AUC 0-24 hours in the preclinical species.

Species	Route	Dose mg/kg/day	#Animals/dose level	Duration	Findings
<b>Pharmacokinetic study in rats (94067)</b>					
Sprague Dawley	Oral (gavage)	60	5/sex	14 days	This study was conducted to provide an estimate of the pharmacokinetic exposure of rats over 24 hours. Plasma concentrations of sildenafil were higher in females than in males, while concentrations of the metabolite, UK-103,320, were higher in males than in females.
<b>Oral toxicity and carcinogenicity study in mice (95007)</b>					
CD1	Oral (gavage)	3 10 30	55/sex	<u>3 &amp; 10 mg:</u> males 649 days females 558 days  <u>30 mg:</u> males 453 days females 404 days	<p>The exposure to the parent compound and the demethylated metabolite, UK-103,320 was dose-related. The compound produced an increase in mortality rate with consequent decreases in survival times and percent of survival.</p> <p>The effect was marked at the mid dose in females and at the high dose in both sexes. In addition, the percent of survival was also slightly decreased in mid-dose males, at the end of the study. Because of the lower survival in mid- and high-dose animals interim sacrifices were decided. When the survival in the high-dose group reached about 20%, the survivors were sacrificed, on day 405 (females) or 454 (males). Control, low- and mid-dose groups were sacrificed on day 559 (females) or 650 (males), when the survival at the mid dose was about 20%. In a number of animals, especially high-dose males (40%), unscheduled death was preceded by abdominal swelling and/or dyspnea. Gastrointestinal dilation and gavage accident were identified as causes of unscheduled death related to treatment. Additionally, the number of deaths without explanatory macroscopic or histopathological changes was higher in mid- and high-dose groups than in the control groups. In high-dose males and females, there was also a trend to body weight decrease compared to controls (10 and 18%, respectively). In addition, there was an abrupt body weight loss in most animals dying prematurely which was more marked in mid- and high-dose females. The treatment produced no increase in the incidence of neoplastic lesions. Furthermore, in the animals sacrificed at the various interim and final sacrifices, there were no differences in the incidence of non-neoplastic lesions between control and treated groups.</p> <p>In conclusion, the doses of 10 and 30 mg/kg produced signs of toxicity consisting mainly of a dose-related increase in mortality. At the dose of 3 mg/kg, although there was no compound effect on group mortality, 2 animals died from gastrointestinal dilation. There were no carcinogenic effects at any dose.</p>
<b>24-Month oral toxicity and carcinogenicity study in rats study (94092)</b>					
Sprague-Dawley	Oral (gavage)	1.5 5 60	60/sex	24 month	<p>The rats were exposed to plasma concentrations of sildenafil and UK-103,320 that increased with dose levels. Male rats were exposed predominantly to UK-103,320, whereas unchanged drug was the major circulating form in females. Overall, the total exposure to drug and metabolite was higher in females than in males.</p> <p>The treatment produced no mortality. Survival at the end of the study ranged between 18 and 42% in males and between 15 and 25% in females.</p> <p>The body weight was decreased in high-dose animals, compared to controls. A transient decrease in body weight occurred also in mid-dose females. There was a dose-related decrease in plasma bilirubin which, in our view, is related to the enzyme-inducing properties of the compound. In high-dose males there was an increased incidence of proliferative changes in the thyroid which was mainly related to an increase in follicular cell hyperplasia. We consider that these changes are the consequence of an increased turnover of thyroid hormones due to hepatic enzyme induction and bear no relevance to man.</p> <p>To conclude, the dose of 60 mg/kg was associated with a toxicologically significant decrease in body weight and with an increase in follicular proliferative changes in the thyroid in males. At 5 mg/kg there was only an inconsistent decrease in the body weight of females. There were no compound effects at 1.5 mg/kg. There were no indications of a carcinogenic potential of sildenafil.</p>

Mutagenicity studies (90817-01/02)			
Study Type	Strain	Dose	Results
<i>in vitro</i> bacterial mutagenicity	<i>S. typhimurium</i> TA 1535, 1537, 98, 100	0.002 - 1 mg/plate	negative
<i>in vitro</i> mammalian cell mutagenicity	Chinese Hamster Ovary / HGPRT	65-240 µg/mL	negative
<i>in vitro</i> clastogenicity	Human lymphocytes	10, 20, 25 µg/mL -S9 100, 125, 250 µg/mL + S9	negative
<i>in vivo</i> clastogenicity	Mouse bone marrow	0, 500, 1000, 2000 mg/kg	negative

### **Reproduction and Teratology**

No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 32 and 68 times the RHD on a mg/m<sup>2</sup> basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the non-pregnant rat the AUC at this dose was about 24 times unbound human AUC.

Species	Route	Dose mg/kg/day	#Animals/dose level	Duration	Findings
<b>Maternal toxicity study in rats by the oral route (92020)</b>					
Sprague-Dawley	Oral (gavage)	10 50 200	7 females	Gestation days 6-17	Hematological, biochemical (plasma) and pathological changes were recorded only at 200 mg/kg. Hematological changes consisted of a moderate decrease in hemoglobin, red blood cell count and packed cell volume accompanied by an increase in the mean red blood cell distribution width. The only variation observed in plasma chemistry was a decrease in mean plasma triglycerides. Finally, a mild hepatic weight increase with hepatic centrilobular hypertrophy was noted after pathological examination. With regard to the fetuses, there was a decrease in the mean male body weight at 200 mg/kg. In male fetuses at 10 and 50 mg/kg and in female fetuses at all dose levels, the mean body weights were similar to those of the control group.  The NOAEL was 50 mg/kg in dams and fetuses given the changes in plasma chemistry and fetal weight of males at 200 mg/kg.
<b>Study of fertility and early embryonic development to implantation in rats by the oral route (94081)</b>					
Sprague-Dawley	Oral (gavage)	3 12 60	20/sex	<u>Males:</u> from 9 weeks before mating to gestation day 20 <u>Females:</u> from 2 weeks before mating to gestation day 6	The treatment produced no adverse effects on the fertility of either sex. In addition, there was no evidence of maternal, embryo- or fetotoxicity. The only finding was a moderate reduction in plasma triglycerides in females treated with 60 mg/kg. Therefore the NOAEL in this study was 60 mg/kg.

Species	Route	Dose mg/kg/day	#Animals/dose level	Duration	Findings
<b>Study for effects on pre- and post-natal development, including maternal function, in rats by the oral route (95068/95095)</b>					
Sprague-Dawley	Oral (gavage)	10 30 60	20 females	from gestation day 6 until 20 days after birth	<p>The only noteworthy finding was a toxicologically significant decrease in the ratio of viable pups at birth, with consequently a decreased litter size of viable pups, at 60 mg/kg. At this high-dose level, there was a toxicologically significant decrease in the 4-day survival index, in the F1 pups body weight on day 1 p.p. and some delay in a developmental landmark, the appearance of upper incisors. There were no findings in the reproductive function of the F1 generation, and in the F2 generation.</p> <p>The NOAEL was 30 mg/kg for F0 females and F1 pups, given the minimal maternal toxicity and the effect on pup development during the first 2 weeks of life. The NOAEL for the F2 generation is 60 mg/kg.</p>
<b>Study for effects on embryo-foetal development in rats by the oral route (95058/95059)</b>					
Sprague-Dawley	Oral (gavage)	10 50 200	20 females	Gestation days 6-17	<p>There were detectable levels of sildenafil and UK-103,320 in maternal plasma, amniotic fluid and fetal homogenates at all dose levels. Treatment at 200 mg/kg produced salivation and a reduction in mean body weight gain between days 6 and 9 p.c., accompanied by a decrease in food intake on day 9 p.c. On day 18 p.c., the mean food consumption increased. Hematological changes consisted of a slight decrease in hemoglobin, red blood cell count and hematocrit accompanied by an increase in the mean red blood cell distribution width at 200 mg/kg. A dose-related increase in the reticulocyte count was present, reaching statistical significance at the high-dose only. The only variation in plasma chemistry was a dose-related decrease in mean plasma triglycerides, at most moderate and statistically significant at the high-dose only. The body weight of male fetuses was reduced at 200 mg/kg. There were no treatment-related external, skeletal or visceral anomalies.</p> <p>Treatment with 200 mg/kg produced a slight maternal toxicity without embryotoxicity but a slight toxicity in male fetuses only. There was no maternal, fetal or embryotoxicity after treatment with 10 or 50 mg/kg. There were no teratological effects at any dose.</p> <p>The NOAEL in this study was 50 mg/kg in dams and fetuses, given the slight toxicity at 200 mg/kg.</p>

### **Rabbits:**

Species	Route	Dose mg/kg/day	#Animals/dose level	Duration	Findings
<b>Maternal toxicity study in rabbits by the oral route (95003/95004)</b>					
New Zealand White	Oral (gavage)	50 100 200	7 females	Gestation days 6-18	<p>Pregnant females and fetuses were exposed to the drug. The only noteworthy findings in dams were an increase in plasma glucose and a decrease in plasma cholesterol at the high dose. This is indicative of a minimal toxicity in dams. There were no adverse effects on embryo or fetal development.</p> <p>The NOAEL was 100 mg/kg in dams given the changes in plasma chemistry values at 200 mg/kg. The NOEL was 200 mg/kg in the developing embryos and fetuses.</p>
<b>Study for effects on embryo-foetal development in rabbits by the oral route (95043/44)</b>					
New Zealand White	Oral (gavage)	10 50 200	20 females	Gestation days 6-18	<p>Sildenafil and UK-103,320 were found in the plasma of pregnant females. The presence of sildenafil was also detected in amniotic fluid. At the high-dose, there were reductions in body weight and body weight gain late in gestation, compared to the control group, which are indicative of minimal maternal toxicity. A reduction in food intake in high-dose females during the same period may have contributed to the body weight changes. The plasma chemistry changes, encountered in the preliminary study, were not found in this study. The treatment had no adverse effects on the developing conceptus.</p> <p>The NOAEL in this study was 50 mg/kg for dams, given the effect on body weight at 100 mg/kg. The NOEL was 100 mg/kg in the developing embryos and fetuses.</p>

**Special Studies:**

Species	Route	Dose mg/kg/ day	#Animals/ dose level	Duration	Findings
<b>Antigenicity study in guinea pigs (95-29-81)</b>					
Hartley Guinea Pigs	Oral	4 mg/mL 20 mg/mL	5/group	N/A	In the active systemic anaphylaxis test, male guinea pigs that received daily doses of 4 or 20 mg/kg sildenafil orally 5 days a week for 3 weeks showed no signs of systemic anaphylaxis reactions after intravenous injection of sildenafil 19 days later as challenge antigen. Similarly, when male guinea pigs sensitized subcutaneously with 2 or 10 mg sildenafil/guinea pig (given on 4 occasions at 1 week intervals) were challenged 16 days later with intravenous injection of sildenafil, they showed no signs of systemic anaphylaxis.  In the passive cutaneous anaphylaxis test, guinea pigs were challenged with sildenafil (30 mg/guinea pig). No positive PCA reactions were observed against anti-sera obtained from guinea pigs immunized orally or subcutaneously with sildenafil.
	sub-cutaneous (with Freund's complete adjuvant)	2 mg/mL 10 mg/mL			
<b>Intra-arterial irritation in rabbits (91073)</b>					
New Zealand White	Intra-arterial	1 mg/animal	4 females	1 day	Sildenafil (1 mg/animal) was administered into the central ear artery of rabbits in a volume of 0.5 mL to examine the potential irritant reactions. The single injection produced no arterial irritation over a 21-day observation period.

## REFERENCES

1. Agelink MW, Schmitz T, Rembrink K, et al. Cardiovascular effects of sildenafil citrate (Viagra<sup>®</sup>): A naturalistic cross-over study. *Eur J Med Res* 2001;6(11):459-64.
2. Arruda-Olson AM, Mahoney DW, Nehra A, et al. Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease. *JAMA* 2002; 287(6):719-25.
3. Ballard SA, Burslem FMF, Gingell CJC, et al. In vitro profile of UK-92,480, an inhibitor of cyclic GMP-specific phosphodiesterase 5 for the treatment of male erectile dysfunction. *J Urol* 1996;155(No 5, Suppl):1462.
4. Ballard SA, Gingell, CJ, Tang K, et al. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol* 1998;159(6):2164-71.
5. Bernard F, Carrier S, Lee JC, Talwar V, Defoy I. Men with Mild Erectile Dysfunction Benefit from Sildenafil Treatment. *J Sex Med* 2010; 7: 3725-3735.
6. Boolell M, Allen MJ, Ballard SA, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996;8(2):47-52.
7. Boshier A, Wilton LV, Shakir SA. Evaluation of the safety of sildenafil for male erectile dysfunction: experience gained in general practice use in England in 1999. *BJU Int.* 2004; 93(6): 796-801.
8. Bush, HS. Safe use of sildenafil in patients with coronary artery disease. *Cleve Clin J Med*, 2001; 68(4):349-52.
9. Buvat J, Gingell CJ, Jardin A, et al. Sildenafil (Viagra<sup>™</sup>), an oral treatment for erectile dysfunction: a 1-year, open-label, extension study. *J Urol* 1997;157(4 Suppl):204.
10. Carson C, Burnett A, Levine L, et al. The efficacy of sildenafil citrate (Viagra<sup>®</sup>) clinical populations: an update. *Urology* 2002; 60 (2B Suppl): 12-27.
11. Carter AJ, Ballard SA and Naylor AM. Effect of selective phosphodiesterase type 5 inhibitor sildenafil on erectile function in the anesthetized dog. *J Urol* 1998;160(1):242-6.
12. Chang G, Hermann HC. Issues and recommendations for treating erectile dysfunction in men with ischemic heart disease. *Cardiovasc Rev Rep* 2001;22(5):285-91.

13. Chuang AT, Strauss JD, Murphy RA, et al. Sildenafil, a type-5 GMP phosphodiesterase inhibitor, specifically amplifies endogenous cGMP-dependent relaxation in rabbit corpus cavernosum smooth muscle in vitro. *J Urol* 1998;160(1):257-61.
14. DeBusk RF, Pepine CJ, Glasser DB, et al. Efficacy and safety of sildenafil citrate in men with erectile dysfunction and stable coronary artery disease. *Am J Cardiol* 2004;93:147-53.
15. Derry F, Gardner BP, Glass C, et al. Sildenafil (Viagra™): a double-blind, placebo-controlled, single-dose, two-way crossover study in men with erectile dysfunction caused by traumatic spinal cord injury. *J Urol* 1997;157(4 Suppl):181.
16. Derry F, Glass C, Dinsmore WW, et al. Sildenafil (Viagra™): An oral treatment for men with erectile dysfunction caused by traumatic spinal cord injury - A 28-day, double-blind, placebo-controlled, parallel-group, dose-response study. 49th Annual Meeting of the American Academy of Neurology. April 12-19, 1997; Boston, Massachusetts, USA. *Neurology* 1997;48(3 Suppl.2):A215.
17. Dogterom P, Zbinden G. Cardiotoxicity of Vasodilators and Positive Inotropic/Vasodilating Drugs in Dogs: An Overview. *Critical Reviews in Toxicology*, 22:203-241(1992).
18. Eardley I, Morgan RJ, Dinsmore WW, et al. UK-92,480, a new oral therapy for erectile dysfunction, a double-blind, placebo controlled trial with treatment taken as required. *J Urol* 1996; 155(No 5, Suppl):495A.
19. Eardley I, Ellis P, Boolel M, et al. Onset and duration of action of sildenafil citrate for the treatment of erectile dysfunction. *Br J Clin Pharmacol* 2002;53:61S-65S.
20. Fox KM, Thadani U, Ma PTS, et al. Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. *Eur Heart J* 2003;24:2206-12.
21. Gingell C, Jardin A, Olsson A, et al. UK-92,480, a new oral treatment for erectile dysfunction: a double-blind, placebo-controlled, once daily dose response study. *J Urol* 1996;155(No 5,Suppl):495A.
22. Gingell C, Sultana S, Wulff M, et al. Duration of action sildenafil citrate in men with erectile dysfunction. *J Sex Med* 2004; 1: 179-84.
23. Glass C, Derry F, Dinsmore WW, et al. Sildenafil (VIAGRA™): an oral treatment for men with erectile dysfunction caused by traumatic spinal cord injury - a double-blind, placebo- controlled, single-dose, two-way crossover study using RigiScan. *J Spinal Cord Med* 1997;20:145. American Spinal Injury Association Annual Meeting; March 24-26, 1997; Houston, TX.
24. Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med* 1998;338(20):1397-404.

25. Guay AT, Perez JB, Jacobson J, et al. Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. *J Androl* 2001;22(5):793-7.
26. Hatzichristou DG. Sildenafil citrate: lessons learned from 3 years of clinical experience. *Int J Impot Res* 2002;14(Suppl 1):S43-S52.
27. Hayes TJ, Roberts GKS, Halliwell WH. An Idiopathic Febrile Necrotizing Arteritis Syndrome in the Dog: Beagle Pain Syndrome. *Toxicologic Pathology* 1989;17:129-37.
28. Herrmann HC, Chang G, Klugherz BD, et al. Hemodynamic effects of sildenafil in men with severe coronary artery disease. *N Engl J Med* 2000;342:1622-6.
29. Jackson, G. Sildenafil (Viagra™): new data, new confidence in treating erectile dysfunction in the cardiovascular patient. *IJCP* 2002;56(2);75.
30. Jetter A, Kinzing-Schippers M, Walchner-Bonjean M, et al. Sildenafil bioavailability is moderately increased by grapefruit juice. *Eur J Clin Pharmacol* 2001;57(8):A35 (abstract).
31. Jetter A, Kinzing-Schippers M, Walchner-Bonjean M, et al. Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* 2002;71(1):21-9.
32. Kloner, RA, Zusman RM. Cardiovascular effects of sildenafil citrate and recommendations for its use. *Am J Cardiol* 1999;84 (5B):11N-17N.
33. Kloner RA. Cardiovascular risk and sildenafil. *Am J Cardiol* 2000;86(2A): 57F-61F.
34. Kloner RA, Morris B, Prisant LM, et al. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hyperten* 2001;14:70-3.
35. Krenzelok, EP. Sildenafil: clinical toxicology profile. *J Clin Toxicol* 2000;38(6):645-51.
36. Langtry, HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999;57(6):967-89.
37. Laties AM, Fraunfelder FT. Ocular safety of Viagra. *Trans Am Ophthalmol Soc* 1999;97:115-25.
38. Lee JC, Bernard F, Carrier S, Talwar V, Defoy I. Do Men with Mild Erectile Dysfunction have the Same Risk Factors as the General Erectile Dysfunction Clinical Trial Population? *BJU International* 2010 Oct. 15 [Epub ahead of print].
39. Lue TF, Sildenafil Study Group. A study of Sildenafil (Viagra™), a new oral agent for the treatment of male erectile dysfunction. 92nd Annual Meeting of the American Urological



- Association. April 12-17, 1997; New Orleans, Louisiana, USA. *J Urol* 1997; 157(4 Suppl):181.
40. McCullough A, Barada J, Fawzy A, et al. Achieving treatment optimisation with sildenafil citrate (Viagra<sup>®</sup>) in patients with erectile dysfunction. *Urology* 2002; 60 (2B Suppl): 28-38.
  41. Morales A, Gingell, C, Collins M, et al. Clinical safety of oral sildenafil citrate (VIAGRA<sup>™</sup>) in the treatment of erectile dysfunction. *Int J Impot Res* 1998;10:69-74.
  42. Morales A, Gajewski JB, Pommerville PJ, et al. 3-year efficacy and safety of Viagra<sup>®</sup> in men with erectile dysfunction: results of Canadian long-term extension study. *Can J Urol* 2003; 10(3):1826 [abstract].
  43. Moreland RB, Goldstein I, Traish A. Sildenafil, a novel inhibitor of phosphodiesterase type 5 in human corpus cavernosum smooth muscle cells. *Life Sci* 1998;62(20):309-18.
  44. Muirhead GJ, Allen MJ, James GC, et al. Pharmacokinetics of sildenafil (Viagra<sup>™</sup>), a selective cGMP PDE5 inhibitor, after single oral doses in fasted and fed healthy volunteers. *Br J Clin Pharmacol* 1996;42(No 2):268P.
  45. Muirhead GJ, Faulkner S, Harness JA, et al. The effects of steady-state erythromycin and azithromycin on the pharmacokinetics of sildenafil citrate in healthy volunteers. *Br J Clin Pharmacol* 2002;53:37S-43S.
  46. Muller, JE. Triggering of Cardiac events by sexual activity: findings from crossover analysis. *Am J Cardiol* 2000;86(2A):14F-18F.
  47. Olson, AM, Persson CA. Efficacy and safety of sildenafil citrate for the treatment of erectile dysfunction in men with cardiovascular disease. *Int J Clin Pract* 2001;55(3):171-6.
  48. Osterloh, I, Eardley, I, Carson, C, et al. Sildenafil: A selective phosphodiesterase (PDE)5 inhibitor in the treatment of erectile dysfunction (ED). In: Carson, C., Kirby, R., Goldstein, I., eds. *Textbook of Erectile Dysfunction*. Oxford, UK: Isis Media LTD; 1999: 285-307.
  49. Padma-Nathan H, Steers WD, Wicker PA. Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. *Int J Clin Pract* 1998;52(6):1-5.
  50. Padma-Nathan H, Eardley I, Kloner R, et al. A 4-year update on the safety of sildenafil citrate (Viagra<sup>®</sup>). *Urology* 2002; 60 (2B Suppl): 67-90.
  51. Partizi R, Leonardo F, Pelliccia F, et al. Effect of sildenafil citrate upon myocardial ischemia in patients with chronic stable angina in therapy with beta-blockers. *Ital Heart J* 2001;2(11):841-4.

52. Pfizer Dept. of Medicine. Sildenafil (Viagra<sup>®</sup>): A new drug in trial for the treatment of erectile dysfunction. *Urologe [B]* 1997;37:51.
53. Piccirillo G, Nocco M, Lionetti M, et al. Effects of sildenafil citrate (Viagra) on cardiac repolarization and on automatic control in subjects with chronic heart failure. *Am Heart J* 2002;143(4):703-10.
54. Pickering T, Shepard A, Puddey I, et al. Sildenafil citrate for erectile dysfunction in men receiving multiple antihypertensive agents - a randomized controlled trial. *Am J Hypertens* 2004; 17:1135-42.
55. Price D, Wareham K, Gingell CJ, et al. Sildenafil (Pfizer UK-92,480), a novel oral treatment for erectile dysfunction (ED) in patients with diabetes. *Diabetes* 1996; 45(Suppl 2):6A.
56. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49(6):822-30.
57. Shakir SAW, Wilton LV, Boshier A, et al. Cardiovascular events in users of sildenafil: results from first phase of prescription event monitoring in England. *B Med J* 2001; 322:651-2.
58. Steers W, Guay AT, Leriche A, et al. Assessment of the efficacy and safety of Viagra<sup>®</sup> (sildenafil citrate) in men with erectile dysfunction during long-term treatment. *Int J Impot Res* 2001;13:261-7.
59. Steif CG, Ückert S, Becker AJ, et al. The effect of the specific phosphodiesterase (PDE) inhibitors on human and rabbit cavernous tissue in vitro and in vivo. *J Urol* 1998;159(4):1390-3.
60. Terrett NK, Bell AS, Brown D, et al. UK-92,480, a potent and selective inhibitor of type V<sub>A</sub> cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction. *Abstr Papers Am Chem Soc* 1995; 210 Meet(Pt 2):MED 229.
61. Terrett NK, Bell AS, Brown D, et al. Sildenafil (Viagra<sup>™</sup>), a potent and selective inhibitor of type 5 GMP phosphodiesterase with utility for the treatment of male erectile dysfunction. *Bioorganic & Medicinal Chemistry Letters* 1996; 6(15): 1819-24.
62. Vitezic, D. A risk-benefit assessment of sildenafil in the treatment of erectile dysfunction. *Drug Safety* 2001; 24(4): 255-65.
63. Warrington, JS, Shader, RI, von-Moltke, LL, et al. In vitro biotransformation of sildenafil (Viagra): identification of human cytochromes and potential drug interactions. *Drug Metab Dispos* 2000; 28(4):392-7.
64. <sup>Pr</sup>VIAGRA Product Monograph (Pfizer Canada Inc.) Revision date: April 12, 2011, Control Number: 144432.

**PART III: CONSUMER INFORMATION**

**Pr<sup>r</sup>Dom-SILDENAFIL  
Sildenafil tablets (as sildenafil citrate)**

This leaflet is part III of a three-part "Product Monograph" published when Dom-SILDENAFIL was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dom-SILDENAFIL. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

Dom-SILDENAFIL (sildenafil citrate) is a treatment for erectile dysfunction in male adults. This is when a man cannot achieve or maintain a hard, erected penis for satisfactory sexual activity.

It is important to note that **Dom-SILDENAFIL works only with sexual stimulation.** Dom-SILDENAFIL alone does not increase your sex drive.

**What it does:**

Dom-SILDENAFIL belongs to a class of medicine called phosphodiesterase type 5 (PDE5) inhibitors. Following sexual stimulation, Dom-SILDENAFIL works by helping to relax the blood vessels in your penis by allowing blood to flow into your penis. This results in improved erectile function.

**When it should not be used:**

- If you are taking any medicines containing nitrates in any form (oral, sublingual [under the tongue], skin patch, or by inhalation [spray]). Although Dom-SILDENAFIL is used occasionally, nitrates must never be used. Nitrates are found in many prescription medicines that are used in the treatment of angina pectoris (chest pain due to heart disease), such as nitroglycerin, isosorbide mononitrate, or isosorbide dinitrate. If you do not understand what nitrates are, or are unsure about whether a medication you are taking is a "nitrate", ask your doctor or pharmacist.

**If you take Dom-SILDENAFIL with nitrate-containing medicines or any other nitrates (e.g., amyl nitrite "poppers"), your blood pressure could suddenly drop to a life-threatening level. You could get dizzy, faint, or even have a heart attack or stroke.**

- If you have ever had an allergic reaction to sildenafil citrate or the non-medical ingredients in Dom-SILDENAFIL.
- Dom-SILDENAFIL is not to be used in men for whom sexual activity is inadvisable.

**What the medicinal ingredient is:**  
sildenafil citrate.

**What the nonmedicinal ingredients are:**  
colloidal silicon dioxide, corn starch, FD&C Blue No.2 aluminum lake, hydroxypropyl methylcellulose, hypromellose, lactose, macrogol, magnesium stearate, polyethylene glycol, povidone, sodium lauryl sulphate, sodium starch glycolate, titanium dioxide.

**What dosage forms it comes in:**

**Tablets:** 25 mg, 50 mg, and 100 mg

**WARNINGS AND PRECAUTIONS**

**This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.**

**BEFORE you use Dom-SILDENAFIL talk to your doctor or pharmacist if you:**

- have heart problems (irregular heart beats, angina, chest pain, or had a heart attack). If you have heart problems, ask your doctor if your heart is healthy enough to handle the extra strain of having sex. If you have chest pain, dizziness or nausea during sex, stop exerting yourself. You should **not** use nitrates but you should seek immediate medical assistance.
- are 65 years of age or over
- have had a stroke
- have low blood pressure or uncontrolled high blood pressure
- have liver or kidney problems
- have sickle cell anemia (abnormality of the red blood cells), multiple myeloma (cancer of the bone marrow) or leukaemia (cancer of the white blood cells)
- are allergic to sildenafil or any of the other ingredients of Dom-SILDENAFIL tablets
- have a deformed penis or Peyronie's disease
- have ever had an erection that lasted more than 4 hours

## IMPORTANT: PLEASE READ

- have stomach ulcers or other bleeding problems.
- have a rare inherited eye disease called retinitis pigmentosa
- Ever had temporary, decrease, or permanent loss of vision, including a condition called Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION). The specific type of vision decrease or loss, called non-arteritic anterior ischemic optic neuropathy (NAION), seems to occur rarely when blood flow to the optic nerve is reduced or blocked. Vision decrease or loss may be partial or complete, in one or very occasionally both eyes. While in some cases the condition may improve over time, it can also be irreversible. Rare cases of central serous chorioretinopathy (serous detachment of the macula layers of the retina ) have been reported.
- Rare but serious skin reactions of Stevens-Johnson's Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported during the post-marketing period.

Dom-SILDENAFIL is not recommended for use in children under 18 years of age and in women.

Dom-SILDENAFIL does not protect against sexually transmitted diseases (STD), including Human Immunodeficiency Virus (HIV).

Alcohol consumption may decrease the ability to get an erection.

Patients should know how to react to the drug before operating a motor vehicle or any machinery.

If you are taking Dom-SILDENAFIL and experience temporary, decrease, or permanent loss of vision, stop taking Dom-SILDENAFIL and call your doctor.

In case of chest pain occurring during or after sexual activity you should not use nitrates but you should seek immediate medical assistance.

Sudden decrease or loss of hearing has been reported in a few number of postmarketing and clinical trial cases with the use of PDE5 inhibitors, including Dom-SILDENAFIL. It has not been established whether these are related directly to the use of these medications or to other factors. If you experience these symptoms, stop taking Dom-SILDENAFIL and call your doctor.

### INTERACTIONS WITH THIS MEDICATION

You should tell your doctor or pharmacist about any other medications that you are taking. Dom-SILDENAFIL may interfere with some drugs. Only take

Dom-SILDENAFIL with other drugs if recommended by your doctor.

### Drugs that may interact with Dom-SILDENAFIL include:

- any drugs that contain nitrates in any form (oral, sublingual [under the tongue], skin patch or by inhalation [spray]). Nitrates are found in many prescriptions that are used to treat angina pectoris (chest pain due to heart disease). You should not take Dom-SILDENAFIL if you are taking these drugs.
- alpha-blockers (drugs used to treat prostate problems or high blood pressure).
- ketoconazole or itraconazole (drugs used to treat fungal infections).
- erythromycin (a drug used to treat bacterial infections)
- ritonavir, saquinavir or other drugs for the treatment of HIV.
- cimetidine (a drug generally used to treat duodenal or gastric problems).

Grapefruit juice may increase the levels of Dom-SILDENAFIL in your blood.

### PROPER USE OF THIS MEDICATION

#### Usual dose:

Your doctor can determine the dose that works best for you. Always take Dom-SILDENAFIL as prescribed by your doctor. You should speak with your doctor or pharmacist if you are unsure. A dose above 100 mg per day is not recommended.

Swallow the tablet whole, with some water.

You should **not** take more than one dose of Dom-SILDENAFIL per day.

If you have serious liver or kidney problems or you are 65 years of age or over, your doctor may start you at the lowest dose (25 mg) of Dom-SILDENAFIL.

#### How to optimize your use of Dom-SILDENAFIL:

You should take Dom-SILDENAFIL approximately 30 to 60 minutes before sexual activity. You can engage in sexual activity within 30 minutes of taking the tablet and for up to 4 hours. The amount of time it takes to have an

**IMPORTANT: PLEASE READ**

effect varies slightly from person to person. Remember, sexual stimulation is required for Dom-SILDENAFIL to work.

You should avoid excessive drinking of alcohol, since alcohol can temporarily impair the ability to get an erection.

Dom-SILDENAFIL can be taken with or without food. However, you may find that it takes longer for Dom-SILDENAFIL to work if you take it with a high-fat meal.

Dom-SILDENAFIL may not work the first time or every time. If Dom-SILDENAFIL did not work for you on one occasion, try again on another day. You will learn how well Dom-SILDENAFIL works for you through your personal experience. The first few times may be charged with emotion or anxiety. If after a few separate attempts, you do not get the results you expect, talk to your doctor.

**Overdose:**

You should **not** take more than one dose of Dom-SILDENAFIL per day. If you have taken more Dom-SILDENAFIL than you should, contact your doctor or a poison control centre immediately.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

As with most drugs, Dom-SILDENAFIL can cause some side effects. These effects are usually mild to moderate in nature and do not last for a long time.

The most common side effects are headache and facial flushing. Less commonly reported side effects are indigestion, dizziness, stuffy nose, effects on vision (including colour tinge, increased brightness of light and blurred vision), seizure, seizure recurrence, sudden decrease or loss of hearing and transient global amnesia (temporary memory loss).

In extremely rare instances, a man may have an erection that lasts many hours. You should call a doctor immediately if you ever have an erection that lasts more than 4 hours.

Reports of sudden loss of vision have occurred rarely with the use of oral erectile dysfunction medications (PDE5 inhibitors). It has not been established whether these are related directly to the use of these medications or to other factors. There may be an increased risk to patients who have already experienced condition called Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION). You should stop taking Dom-SILDENAFIL

and consult your doctor if you experience a decrease in, or loss of, vision in one or both eyes.

Reports of serious skin reactions characterized by rash, blisters, peeling skin and pain, which require immediate medical attention, have also occurred rarely. You should stop taking Dom-SILDENAFIL V and consult your doctor if you experience such reactions.

If you notice any side effects not mentioned above, or any of the above-mentioned side effects persist or become bothersome, please contact your doctor or pharmacist.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>			
Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
headache	✓		
facial flushing	✓		
indigestion	✓	✓	
dizziness	✓		
stuffy nose	✓		
effects on vision *	✓		
allergic reactions +			✓
prolonged erection			✓
serious skin reactions characterized by rash, blisters, peeling skin and pains			✓

\* including colour tinge, increased brightness of light and blurred vision.

+ An allergic reaction can be a rash, itching, a swollen face, swollen lips or shortness of breath. If this ever happens to you, discontinue Dom-SILDENAFIL and notify your doctor or pharmacist

***This is not a complete list of side effects. For any unexpected effects while taking Dom-SILDENAFIL, contact your doctor or pharmacist.***

## HOW TO STORE IT

- Store between 15°C and 30°C, in the original package. Do not freeze.
- Do not take Dom-SILDENAFIL after the expiry date shown on the package.
- Always keep Dom-SILDENAFIL out of reach and sight of children.

## REPORTING SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program

Health Canada

Postal Locator 0701E

Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Dominion Pharmacal. at, 1-888-550-6060.

This leaflet was prepared by

**Dominion Pharmacal.**

Montreal Quebec

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