PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]TARO-SILDENAFIL

Sildenafil Tablets

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

Mfr. Std.

cGMP-Specific Phosphodiesterase Type 5 Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TARO-SILDENAFIL (Sildenafil Tablets) is indicated for:

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- Sildenafil 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 10 CLINICAL PHARMACOLOGY, 4 DOSAGE AND ADMINISTRATION).
- After patients have taken TARO-SILDENAFIL, 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. CLcr < 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.
- Treatments for erectile dysfunction should not be generally used in men for whom sexual activity is inadvisable (see also 7 WARNINGS AND PRECAUTIONS).
- TARO-SILDENAFIL is contraindicated in patients with a known hypersensitivity to any component of the tablet (see 13 PHARMACEUTICAL INFORMATION).

- TARO-SILDENAFIL is contraindicated in patients with erectile dysfunction with previous episode of non-arteritic anterior ischaemic optic neuropathy (NAION) (see 7 WARNINGS AND PRECAUTIONS).
- The co-administration of PDE5 inhibitors, including TARO-SILDENAFIL, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may lead to potentially life-threatening episodes of symptomatic hypotension or syncope.

4 DOSAGE AND ADMINISTRATION

4.1 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 4.2 Recommended Dose and Dose Adjustment, 10 CLINICAL PHARMACOLOGY, 7 WARNINGS AND PRECAUTIONS).

Sildenafil 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 10 CLINICAL PHARMACOLOGY, 2 CONTRAINDICATIONS).

4.2 Recommended Dose and Dosage Adjustment

For most patients, the recommended dose of TARO-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 4.1 Dosing Considerations above, 10 CLINICAL PHARMACOLOGY, 7 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 7 WARNINGS AND PRECAUTIONS).

4.4 Administration

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

TARO-SILDENAFIL tablets should be swallowed whole with water.

5 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 health professional. The treatment of priapism/prolonged erection should be according to established medical practice. Health professional 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 detumesce 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 mcg) 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 detumesce 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets / 25 mg, 50 mg and 100 mg sildenafil (as sildenafil citrate)	calcium hydrogen phosphate (anhydrous), croscarmellose sodium, FD&C Blue #1 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Description

TARO-SILDENAFIL - 25 mg Tablets (sildenafil citrate equivalent to 25 mg of sildenafil per tablet) are supplied as blue coloured, rounded triangular shaped, film-coated tablets, with '**S21**' engraved on one side and plain on the other side, and supplied as follows:

- Blister pack of 4 (1 x 4) tablets

TARO-SILDENAFIL - 50 mg Tablets (sildenafil citrate equivalent to 50 mg of sildenafil per tablet) are supplied as blue coloured, rounded triangular shaped, film-coated tablets, with '**S22'** engraved on one side and plain on the other side, and supplied as follows:

- Bottle of 30 tablets
- Blister pack of 4 (1 x 4) tablets

TARO-SILDENAFIL - 100 mg Tablets (sildenafil citrate equivalent to 100 mg of sildenafil per tablet) are supplied as blue coloured, rounded triangular shaped, film-coated tablets, with '**S23**' engraved on one side and plain on the other side, and supplied as follows:

- Bottle of 30 tablets
- Blister pack of 4 (1 x 4) tablets

7 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 TARO-SILDENAFIL, 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 TARO-SILDENAFIL 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 10 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 9 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, health professionals should advise patients what to do in the event of postural hypotensive symptoms.

Driving and Operating Machinery

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to TARO-SILDENAFIL, before driving or operating machinery. The effect of sildenafil on the ability to drive and use machinery has not been studied.

Ear/Nose/Throat

Sudden decrease or loss of hearing has been reported in a few number of post-marketing and clinical trial cases with the use of PDE5 inhibitors, including sildenafil**.** These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including sildenafil. 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 8 ADVERSE REACTIONS, 8.5 POST-MARKET ADVERSE REACTIONS and PATIENT MEDICATION INFORMATION). Health professionals should advise patients to stop taking TARO-SILDENAFIL and seek prompt medical attention in case of sudden decrease or loss of hearing.

Hematologic

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure. This is of little or no consequence in most patients. However, prior to prescribing sildenafil, health professionals 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 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 had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans (see 10 CLINICAL PHARMACOLOGY).

There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore, TARO-SILDENAFIL 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 10 CLINICAL PHARMACOLOGY, 4 DOSAGE AND ADMINISTRATION).

Ophthalmologic

Patients should stop taking PDE5 inhibitors, including TARO-SILDENAFIL, and consult their health professional immediately if they experience a decrease in, or sudden loss of, vision in one or both eyes. Post-marketing reports of sudden loss of vision have occurred rarely, in temporal association with the use of PDE5 inhibitors. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. PDE 5 inhibitors, including TARO-SILDENAFIL, are not recommended in patients with male erectile dysfunction with a previous episode of NAION (see 2 CONTRAINDICATIONS).

There are no controlled clinical data on the safety or efficacy of sildenafil 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 10 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**.** If this happens, then the patient should not operate a motor vehicle or any heavy machinery until the adverse effects disappear (see 10 CLINICAL PHARMACOLOGY).

Rare cases of central serous chorioretinopathy have been reported during the post-marketing period in temporal association with the use of sildenafil. 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 8.5 POST-MARKET ADVERSE DRUG REACTIONS).

Renal

In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLcr <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.

A starting dose of 25 mg should be considered in patients with severe renal impairment (see 10 CLINICAL PHARMACOLOGY, 4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

Function

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. 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 8 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 TARO-SILDENAFIL with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil (REVATIO), or other agents for the treatment of erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Skin

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

7.1 Special Populations

Women, Nursing Mothers, Pregnancy: TARO-SILDENAFIL is not indicated for use in women. There are no adequate and well-controlled studies in pregnant or lactating women.

7.1.3 Pediatrics

TARO-SILDENAFIL is not indicated for use in children.

7.1.4 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 10 CLINICAL PHARMACOLOGY, 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

During clinical trials, the most commonly observed adverse events associated with the use of sildenafil (incidence of 5% or greater) and observed at a rate on sildenafil at least three times that of placebo were headache (15.8%), flushing (10.5%) and dyspepsia (6.5%). There have been rare post-marketing reports of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and very rare reports of priapism.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Sildenafil 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 (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving sildenafil 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 was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

Table 2. Adverse Events Reported by ≥ 2% of Patients Treated with Sildenafil or Placebo in PRN Flexible-Dose Phase II/III Studies

Adverse Event	Percentage of Patients Reporting Event	
	Sildenafil (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.

8.3 Less Common Clinical Trial Adverse Reactions

The following events occurred in <2% of patients in phase II/III 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, hypernatremia;
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.

Myocardial Infarction and Cardiovascular Mortality

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.

Clinical Trial Adverse Drug Reactions Reported in 74 Double-Blind Placebo-Controlled Phase II/III/IV Studies

When sildenafil was taken as recommended in 74 randomized double-blind, placebo-controlled (DBPC) Phase II/III/IV studies, adverse reactions reported by ≥2% of patients treated with sildenafil (n=9,570) and more frequently than placebo (n=7,237) were headache, flushing, dyspepsia, nasal congestion and dizziness. The nature and frequency of adverse reactions reported by ≥2% of patients in this pooled dataset of 74 DBPC studies was consistent with the adverse reactions reported in the 6 flexible-dose studies detailed above in Table 2.

The following adverse reactions occurred in <2% of patients in the 74 DBPC clinical trials.

Cardiac disorders: palpitations, tachycardia;

Eye disorders: vision blurred, chromatopsia, cyanopsia, photophobia, visual disturbance, photopsia, ocular hyperaemia, eye pain, visual brightness, abnormal sensation in eye, asthenopia, conjunctival hyperaemia, dry eye, erythropsia, eye disorder, eye irritation, eye edema, eyelid edema, eye swelling, halo vision, xanthopsia;

Gastrointestinal disorders: nausea, dry mouth, abdominal pain upper, vomiting, gastroesophageal reflux disease, oral hypoaesthesia;

General conditions and administration site conditions: feeling hot, irritability;

Immune system disorders: hypersensitivity;

Infections and infestations: rhinitis;

Investigations: heart rate increased;

Musculoskeletal and connective tissue disorders: pain in extremity, myalgia;

Nervous system disorders: syncope, somnolence;

Reproductive system and breast disorders: erection increased;

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

Skin and subcutaneous tissue disorders: rash;

Vascular disorders: hot flush, hypotension.

8.5 Post-Market Adverse Reactions

Reports of adverse events temporally associated with sildenafil 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 without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to combination of these factors, or to other factors (see 7 WARNINGS AND PRECAUTIONS).

Central & Peripheral Nervous System: seizure, seizure recurrence, transient global amnesia;

Gastrointestinal: vomiting;

Urogenital: prolonged erection, priapism (see 7 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. 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 , to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS and PATIENT MEDICATION INFORMATION).

Rare cases of central serous chorioretinopathy have been reported during the post-marketing period in temporal association with the use of sildenafil. 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 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Nitrates: see 2 CONTRAINDICATIONS • Guanylate cyclase stimulators, such as riociguat: see 2 CONTRAINDICATIONS.

9.2 Drug Interactions Overview

In vitro studies:

Sildenafil metabolism is principally mediated by the cytochrome P-450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route) (see 10 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 mcM). Given sildenafil peak plasma concentrations of approximately 1 mcM after recommended doses, it is unlikely that TARO-SILDENAFIL 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%.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 3 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Acetylsalicylic acid	CT	sildenafil (50 mg) did not potentiate the increase in bleeding time, measured using a standard simplate method, caused by acetylsalicylic acid (150 mg).	
Alpha-blockers (e.g. doxazosin)	CT	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	Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals (see 7 WARNINGS AND PRECAUTIONS). Some alpha-blockers and antidepressants have reported priapism or prolonged/painful erections in their labels.

Proper/Common name	Source of Evidence	Effect	Clinical comment
		of patients who experienced symptomatic postural hypotension. These reports included dizziness and light-headedness, but not syncope.	
Antacids (e.g. magnesium hydroxide/aluminium hydroxide)	CT	In normal healthy male volunteers, co-administration of single doses of antacid 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.	
Antihypertensives (e.g. 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)	CT	When sildenafil (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 10 CLINICAL PHARMACOLOGY). Patients on multiple antihypertensive medications were included in the pivotal clinical trials for sildenafil. The analysis showed no differences in the adverse effect profile of patients taking sildenafil with and	

Proper/Common name	Source of Evidence	Effect	Clinical comment
		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 10 CLINICAL PHARMACOLOGY).	
Bosentan	CT	Sildenafil at steady state (80 mg three times a day) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg twice a day).	

CYP2C9 Substrate (e.g. tolbutamide, warfarin)	CT	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.	
CYP3A4 Inducers (e.g. rifampin)	T	It can be expected that concomitant administration of CYP3A4 inducers will decrease plasma levels of sildenafil.	
CYP3A4 Inhibitors (e.g. erythromycin, saquinavir, ritonavir, ketoconazole, itraconazole and the non-specific CYP inhibitor cimetidine)	CT	Concomitant use is associated with increased plasma levels of sildenafil (see 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY). When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate 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. In a study of healthy male volunteers, co-administration of the endothelin antagonist bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady state (125 mg twice a day) with sildenafil at steady state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max}, respectively. Sildenafil increased bosentan AUC and C_{max} by 49.8% and 42%, respectively. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil. Cimetidine (800 mg), a cytochrome P-450 inhibitor and a non- specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered	

		with sildenafil (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 (e.g. saquinavir, ritonavir)	CT	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. 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 4 DOSAGE AND ADMINISTRATION).	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Effects of Other Drugs on Sildenafil

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 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.

9.5 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.

TARO-SILDENAFIL can be taken with or without food. However, when sildenafil 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 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sildenafil 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 7 WARNINGS AND PRECAUTIONS).

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 7 WARNINGS AND PRECAUTIONS).

10.2 Pharmacodynamics

Effects of Sildenafil 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 2 CONTRAINDICATIONS).

Effects of Sildenafil on Cardiac Parameters:

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

Effects of Sildenafil on Erectile Response:

Sildenafil 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, respectively, reported an improvement in their erections, compared to 25% on placebo (p <0.0001, see 14 CLINICAL TRIALS).

In eight double-blind, placebo-controlled, cross-over studies using RigiScan® (a device used to objectively measure penile rigidity and duration of erections), erections during sexual stimulation improved significantly on sildenafil 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 approximately 60 minutes post-dose.

All eight studies investigating the effects of sildenafil on penile plethysmography (RigiScan®) 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 increases couples' ability to have sexual intercourse (see 14 CLINICAL TRIALS).

10.3 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 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 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 9 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.

Elimination:

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 7 WARNINGS AND PRECAUTIONS,4 DOSAGE AND ADMINISTRATION).

- **Renal Insufficiency:** In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30- 49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe (CLcr <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.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15° C to 30° C).

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

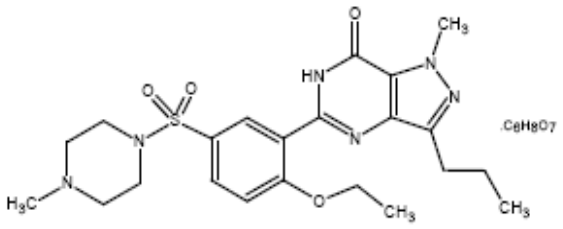
Proper name: sildenafil citrate

Chemical name:

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

Molecular formula and molecular mass: $C_{22}H_{30}N_6O_4S{\cdot}C_6H_8O_7$; 666.70 g/mol

Structural formula:



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

pk_a:	protonation of tertiary amine	6.53
	deprotonation of pyrimidirone moiety	9.17
Partition coefficient:	octanol/water	2.7
Solubility:	Slightly soluble in methanol	

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Study demographics and trial design

Sildenafil 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 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 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.

14.2 Study Results

Sildenafil 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, respectively, reported an improvement in their erections, compared to 25% on placebo (see **Figure 1**).

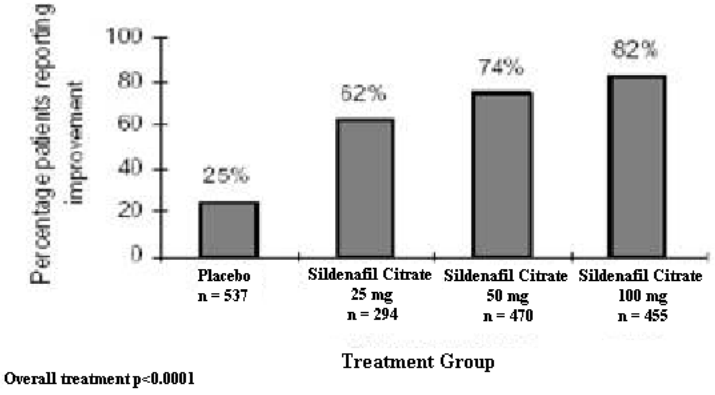


Figure 1 - Percentage of Patients reporting an Improvement in Erections

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 patients reported the following statistically significant changes (see **Figure 2**).

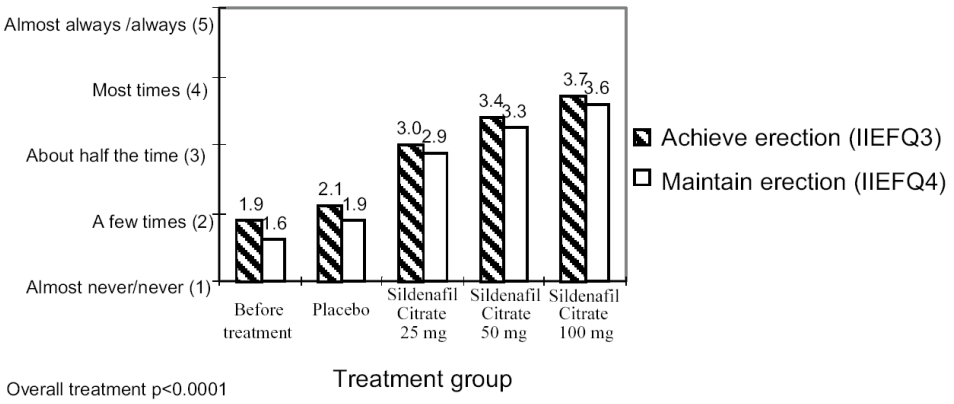


Figure 2 - Effect of Sildenail Citrate on Ability to Achieve and Maintain an Erection Sufficient for Sexual Intercourse

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 restores the values of the domains (**Figure 3**, Bar 2) towards the values of age matched controls without ED (**Figure 3**, Bar 3).

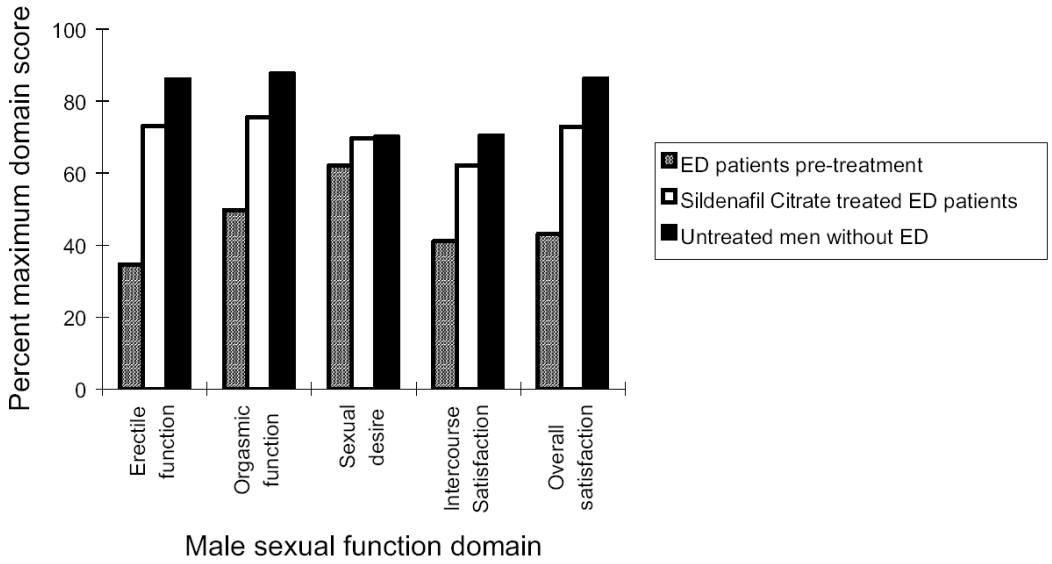


Figure 3 – Effect of Sildenafil on Male Sexual Function Domains of the IIEF

Sildenafil increases couples' ability to have sexual intercourse. With sildenafil, 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 patients with one or more successful attempt at intercourse, 81% of attempts were successful.

The efficacy of sildenafil was maintained over time. In a long-term, open-label trial of 12-month duration, 88% (256/292) of patients reported that sildenafil 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 etiology.

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

Other Patient Populations:

Across all trials, sildenafil 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 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 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 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 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 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 7 WARNINGS AND PRECAUTIONS).

14.3 Comparative Bioavailability Studies

A balanced, randomized, blinded, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing TARO-SILDENAFIL tablets (Sun Pharma Canada Inc.) with [Pr]Viagra® 100 mg Tablets [Pfizer Canada Inc., Kirkland Quebec H9J2M5] in twenty four (24) healthy, adult, male human subjects under fasting conditions.

Out of twenty four (24) subjects enrolled, twenty one (21) subjects completed both periods of the study. Statistical analysis was performed on twenty one (21) subjects completing the study.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Sildenafil (1 X 100 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-T} (ng-hr/mL)	2693.17 2869.67 (38.4)	2559.56 2643.44 (26.5)	105.6	95.8 - 116.4
AUC_{0-I} (ng-hr/mL)	2834.46 3003.72 (37.2)	2617.02 2703.45 (26.5)	107.3	97.6 - 117.9
C_{max} (ng/mL)	970.28 1040.12 (37.7)	904.98 951.41 (30.1)	108.1	90.7 – 128.7
T_{max}[3] (h)	0.66 (0.33 - 2.00)	0.58 (0.25 – 3.00)	-	-
$T_{½}$[4] (h)	4.90 (32.4)	4.65 (32.6)	-	-

[1] TARO-SILDENAFIL Tablets 100 mg (Sun Pharma Canada Inc.)
[2] [Pr] Viagra® 100 mg Tablets (Pfizer Canada Inc., Kirkland Quebec H9J2M5) were purchased in Canada.
[3] Expressed as the median (range)
[4] Expressed as the arithmetic mean (CV%)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Long-Term Toxicity Mice:

Species	Route	Dose mg/kg/ day	#Animals / dose level	Duration	Findings
3-Month oral (gavage) prechronic toxicity study in mice (94049)					
CD1	Oral (gavage)	10 50 100 200	10/sex	3 months	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. The NOAEL in this study was 10 mg/kg, given the mortality and gastrointestinal dilation at higher doses.
Species	**Route**	**Dose mg/kg/ day**	**#Animals / dose level**	**Duration**	**Findings**
3-Month oral (gavage) exploratory toxicity study in mice (94101)					

CD1	Oral (gavage)	20 40 100	10/sex	3 months	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. The NOAEL in this study was 20 mg/kg, given the mortality and gastrointestinal dilation at higher doses.

Long-Term Toxicity - Rats:

Species	Route	Dose mg/kg/ day	#Animals / dose level	Duration	Findings
10-Day oral range-finding toxicity in rats (90080)					
Sprague Dawley	Oral (gavage)	50 150 500	5/sex	10 days	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. The NOAEL in this study was 150 mg/kg, based on the mortality at 500 mg/kg.

Species	Route	Dose mg/kg/ day	#Animals / dose level	Duration	Findings
1-Month oral toxicity in rats (90143)					
Sprague Dawley	Oral (gavage)	10 45 200	10/sex	1 month	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). 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 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.
28-Day oral exploratory toxicity study in rats (94085)					

Sprague-Dawley	Oral (gavage)	0 60 120	10 males/ group	28 days	A 2-year rat carcinogenicity study with sildenafil 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. 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.

=	Route	Dose mg/kg/ day	#Animals / dose level	Duration	Findings
Investigation of the relationship between liver enzyme induction and thyroxine clearance in rats (96010)					
Sprague-Dawley	Oral (gavage)	200	10 females	1 month	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 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. 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. 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.
6-Month oral toxicity study in rats (91098)					

Sprague-Dawley	Oral (gavage)	3 12 60	20/sex	6 months	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. The NOAEL in this study was 60 mg/kg.
13-Day intravenous range-finding in rats (90139)					
Sprague-Dawley	I.V.	2.5 5 10	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 male group. The NOAEL in this study was 10 mg/kg.
1-Month intravenous toxicity study in rats (91044)					
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
10-Day oral range-finding toxicity in dogs (90081)					
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.
1-Month oral toxicity study in dogs (90125)					
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.
6-Month oral toxicity in dogs (91099)					
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.
Species	Route	Dose mg/kg/ day	#Animals / dose level	Duration	Findings
12-Month oral toxicity study in dogs (95039)					

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.
14-Day intravenous range-finding toxicity in dogs (90142)					
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.
1-Month intravenous toxicity in dogs (91041)					
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.

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^2 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 $ng\text{-}h/mx^3$, and compared with the AUC 0-24 hours in the preclinical species.

Species	Route	Dose mg/kg/ day	#Animals/ dose level	Duration	Findings
Pharmacokinetic study in rats (94067)					
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.
Oral toxicity and carcinogenicity study in mice (95007)					
CD1	Oral (gavage)	3 10 30	55/sex	<u>3 & 10 mg:</u> males 649 days females 558 days <u>30 mg</u>: males 453 days females 404 days	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. 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. 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.
Species	**Route**	**Dose mg/kg/ day**	**#Animals/ dose level**	**Duration**	**Findings**
24-Month oral toxicity and carcinogenicity study in rats study (94092)					
Sprague-Dawley	Oral (gavage)	1.5 5 60	60/sex	24 month	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. 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. 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. 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.

Reproductive and Developmental Toxicology

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^2 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
Maternal toxicity study in rats by the oral route (92020)					
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.
Study of fertility and early embryonic development to implantation in rats by the oral route (94081)					
Sprague-Dawley	Oral (gavage)	3 12 60	20/sex	Males: from 9 weeks before mating to gestation day 20 Females: 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.
Study for effects on pre- and post-natal development, including maternal function, in rats by the oral route (95068/95095)					

Sprague-Dawley	Oral (gavage)	10 30 60	20 females	from gestation day 6 until 20 days after birth	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 F_1 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 F_1 generation, and in the F_2 generation. The NOAEL was 30 mg/kg for F_0 females and F_1 pups, given the minimal maternal toxicity and the effect on pup development during the first 2 weeks of life. The NOAEL for the F_2 generation is 60 mg/kg.

Species	Route	Dose mg/kg/ day	#Animals/ dose level	Duration	Findings
Study for effects on embryo-foetal development in rats by the oral route (95058/95059)					
Sprague-Dawley	Oral (gavage)	10 50 200	20 females	Gestation days 6-17	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. 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. The NOAEL in this study was 50 mg/kg in dams and fetuses, given the slight toxicity at 200 mg/kg.

Rabbits:

Species	Route	Dose mg/kg/ day	#Animals/ dose level	Duration	Findings
Maternal toxicity study in rabbits by the oral route (95003/95004)					
New Zealand White	Oral (gavage)	50 100 200	7 females	Gestation days 6-18	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. 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.
Study for effects on embryo-foetal development in rabbits by the oral route (95043/44)					
New Zealand White	Oral (gavage)	10 50 200	20 females	Gestation days 6-18	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. 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Viagra® (Sildenafil Tablets, 25 mg, 50 mg and 100 mg), submission control no. 274068, Product Monograph, BGP Pharma ULC (DEC 27, 2023).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TARO-SILDENAFIL

Sildenafil tablets

Read this carefully before you start taking **TARO-SILDENAFIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TARO-SILDENAFIL.**

What is TARO-SILDENAFIL used for?

TARO-SILDENAFIL is used to treat erectile dysfunction in male adults. Erectile dysfunction is the inability to get or keep an erected penis that is hard enough for sex.

TARO-SILDENAFIL works only with sexual stimulation. TARO-SILDENAFIL alone does not increase your sex drive.

How does TARO-SILDENAFIL work?

TARO-SILDENAFIL works by helping to relax the blood vessels in your penis after being sexually aroused. This allows blood to flow into your penis. This results in improved erectile function.

What are the ingredients in TARO-SILDENAFIL?

Medicinal ingredients: sildenafil (as sildenafil citrate)

Non-medicinal ingredients:

calcium hydrogen phosphate (anhydrous), croscarmellose sodium, FD&C Blue #1 aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

TARO-SILDENAFIL comes in the following dosage forms:

- Tablets: 25 mg, 50 mg or 100 mg sildenafil (as sildenafil citrate).

Do not use TARO-SILDENAFIL if:

- You are taking any medicines containing nitrates in any form (oral, sublingual [under the tongue], skin patch, or by inhalation [spray]).
    - Never take nitrates after using TARO-SILDENAFIL even if you have chest pain. 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 do not understand what nitrates are, or are unsure about whether a medication you are taking is a “nitrate”, ask your healthcare professional.
- You have loss of vision in one or both eyes from an eye disease called non-arteritic anterior ischaemic optic neuropathy (NAION).
- You have ever had an allergic reaction to sildenafil or any other ingredients in TARO-

SILDENAFIL.

- You are not supposed to have sexual activity because of your overall health condition.
- You are taking medication for pulmonary hypertension (guanylate cyclase stimulators), such as riociguat.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TARO-SILDENAFIL. Talk about any health conditions or problems you may have, including if you:

- have heart problems (like irregular heart beats, heart failure, heart disease, heart attack, angina, chest pain).
    - ask your healthcare professional 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. Do **not** use nitrates but you should get medical help right away.
- 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)
- have a deformed penis or other penis problems
- have ever had an erection that lasted more than 4 hours
- have stomach ulcers or other bleeding problems
- have an eye disease called retinitis pigmentosa

Other warnings you should know about:

Eye Problems: TARO-SILDENAFIL may cause a sudden decrease or loss of vision. If this happens, stop taking TARO-SILDENAFIL and tell your healthcare professional right away.

Ear Problems: TARO-SILDENAFIL may cause sudden decrease or loss of hearing, dizziness or ringing in the ears. If you experience these symptoms, stop taking TARO-SILDENAFIL and talk to your healthcare professional.

Driving and using machines: Before you perform tasks, which may require special attention, wait until you know how you respond to TARO-SILDENAFIL. Dizziness or altered vision (colour, light sensitivity, blurry vision, eye pain, red eyes) can occur while using TARO-SILDENAFIL.

Sexual Health:

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

- Tell your healthcare professional right away if you have an erection that lasts longer than 4 hours.
- Drinking alcohol may decrease the ability to get an erection.

Women and children: TARO-SILDENAFIL is not for use in women and children under 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Serious drug interactions with TARO-SILDENAFIL include:

- Any medicines that contain nitrates, used to treat chest pain due to heart disease
- Guanylate cyclase stimulators, used to treat pulmonary hypertension, such as riociguat.

The following may interact with TARO-SILDENAFIL:

- Medicines used to treat prostate problems or high blood pressure (alpha-blockers), such as doxazosin
- Medicines used to treat fungal infections, such as ketoconazole, itraconazole
- Medicines used to treat bacterial infections, such as erythromycin, rifampin
- Medicines used to treat HIV, such as ritonavir, saquinavir
- Medicines used to treat high blood pressure in the blood vessels between the heart and the lungs, like bosentan and other medicines that contain sildenafil
- Cimetidine, a medicine used to treat stomach or digestive problems
- Other medicines used to treat erectile dysfunction
- Grapefruit juice may increase the levels of TARO-SILDENAFIL in your blood
- High fat meals may delay the effect of TARO-SILDENAFIL

How to take TARO-SILDENAFIL:

- Always take TARO-SILDENAFIL as directed by your healthcare professional. Talk to your healthcare professional if you are unsure.
- Take TARO-SILDENAFIL about 30 to 60 minutes before sexual activity. You may take TARO-SILDENAFIL between 30 minutes to 4 hours before sexual activity if needed.
    - The amount of time it takes to have an effect varies slightly from person to person. Sexual stimulation is needed for TARO-SILDENAFIL to work.
- Take with or without food. However, TARO-SILDENAFIL may take longer to work if you take it with a high-fat meal.
- Swallow tablet whole with some water.

Recommended dose:

- **Tablets:** Your healthcare professional can determine the dose that works best for

you.

The maximum dose is 100 mg per day. You should not take more than one dose of TARO-SILDENAFIL per day.

If you have serious liver or kidney problems or you are 65 years of age or over, your healthcare professional may start you at the lowest dose of TARO-SILDENAFIL.

Overdose:

If you think you, or a person you are caring for, have taken too much TARO-SILDENAFIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using TARO-SILDENAFIL?

These are not all the possible side effects you may have when taking TARO-SILDENAFIL. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- headache, facial flushing
- nausea, vomiting, indigestion, abdominal pain, diarrhea
- dizziness
- dry, stuffy, or swollen nose
- throat tightness, dry mouth, decreased sensitivity of the mouth
- pain in arms and legs, myalgia (muscle pain), back pain
- sleepiness/drowsiness
- cold or flu symptoms
- erection increased

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
LESS COMMON			
Ear problems: sudden decrease or loss of hearing, ringing in the ears		√	
Eye problems: colour tinge, blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation, blocked eye veins, eye pressure			√
RARE			
Serious skin reactions: redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			√
VERY RARE			
Priapism: erection lasting more than 4 hours			√
UNKNOWN			
Allergic reactions: rash, hives, itch, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Arrhythmia / tachycardia (abnormal heart rhythms): fast or irregular heart beat, palpitations, heart rate increased, shortness of breath, dizziness			√
Chest pain			√
Cough		√	
Fever		√	

Hypotension (low blood pressure): dizziness, fainting, lightheadedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	√		
Myocardial infarction (heart attack): chest pain or pressure, shortness of breath, jaw, left arm, between the shoulder blades or upper abdomen, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			√
Nosebleeds		√	
Pulmonary Hemorrhage (acute bleeding from the lung): oozing of bloody fluid from the nose and respiratory tract, accompanied by rapid worsening of patient respiration, turning blue and in severe cases, shock)			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Seizures: uncontrollable shaking with or without loss of consciousness			**√**
Shortness of breath		**√**	
Stroke (bleeding in the brain): bleeding in the brain, vision changes, difficulty speaking, weakness on one side of the body, dizziness, lack of coordination or poor balance			**√**
Transient global amnesia (temporary memory loss)		**√**	
Transient ischaemic attack: temporary loss of vision, difficulty speaking, weakness on one side of the body, numbness or tingling usually on one side of the body, dizziness, lack of coordination or poor balance.			**√**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15° C to 30° C), in the original package.
- Do not take TARO-SILDENAFIL after the expiry date shown on the package.
- Always keep TARO-SILDENAFIL out of reach and sight of children.

If you want more information about TARO-SILDENAFIL:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-840-1340.

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