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Sildenafil Tablets USP

XXXXXX

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SILDENAFIL TABLETS safely and effectively. See full prescribing information for SILDENAFIL TABLETS.

SILDENAFIL tablets, for oral use
Initial U.S. Approval: 1998

RECENT MAJOR CHANGES

Warnings and Precautions, Effects on the Eye (5.3) 08/2017

INDICATIONS AND USAGE

Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction (ED) (1)

DOSAGE AND ADMINISTRATION

- For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, sildenafil tablets may be taken anywhere from 30 minutes to 4 hours before sexual activity (2.1)
- Based on effectiveness and toleration, may increase to a maximum of 100 mg or decrease to 25 mg (2.1)
- Maximum recommended dosing frequency is once per day (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 50 mg and 100 mg (3)

CONTRAINDICATIONS

- Administration of sildenafil tablets to patients using nitric oxide donors, such as organic nitrates or organic nitrites in any form. Sildenafil was shown to potentiate the hypotensive effect of nitrates (4.1, 7.1, 12.2)
- Known hypersensitivity to sildenafil or any component of tablet (4.2)
- Administration with guanylate cyclase (GC) stimulators, such as riociguat (4.3)

WARNINGS AND PRECAUTIONS

- Patients should not use sildenafil if sexual activity is inadvisable due to cardiovascular status (5.1)
- Patients should seek emergency treatment if an erection lasts >4 hours. Use sildenafil with caution in patients predisposed to priapism (5.2)
- Patients should stop sildenafil tablets and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non arteritic anterior ischemic optic neuropathy (NAION). Sildenafil tablets should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION. (5.3)
- Patients should stop sildenafil tablets and seek prompt medical attention in the event of sudden decrease or loss of hearing (5.4)
- Caution is advised when sildenafil is co-administered with alpha-blockers or anti-hypertensives. Concomitant use may lead to hypotension (5.5)
- Decreased blood pressure, syncope, and prolonged erection may occur at higher sildenafil exposures. In patients taking strong CYP inhibitors, such as ritonavir, sildenafil exposure is increased. Decrease in sildenafil dosage is recommended (2.4, 5.6)

ADVERSE REACTIONS

Most common adverse reactions (≥ 2%) include headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness and rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Umedica Laboratories USA Inc. at 1-855-288-5777 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Sildenafil can potentiate the hypotensive effects of nitrates, alpha blockers, and anti-hypertensives (4.1, 5.5, 7.1, 7.2, 7.3, 12.2)
- With concomitant use of alpha blockers, initiate sildenafil at 25 mg dose (2.3)
- CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, erythromycin): Increase sildenafil exposure (2.4, 7.4, 12.3)
  - Ritonavir: Do not exceed a maximum single dose of 25 mg in a 48 hour period (2.4, 5.6)
  - Erythromycin or strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, saquinavir): Consider a starting dose of 25 mg (2.4, 7.4)

USE IN SPECIFIC POPULATIONS

- Geriatric use: Consider a starting dose of 25 mg (2.5, 8.5)
- Severe renal impairment: Consider a starting dose of 25 mg (2.5, 8.6)
- Hepatic impairment: Consider a starting dose of 25 mg (2.5, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sildenafil tablets are indicated for the treatment of erectile dysfunction.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, sildenafil tablets may be taken anywhere from 30 minutes to 4 hours before sexual activity. The maximum recommended dosing frequency is once per day.

Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg.

2.2 Use with Food

Sildenafil tablets may be taken with or without food.

2.3 Dosage Adjustments in Specific Situations

Sildenafil tablets was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors such as organic nitrates or organic nitrites in any form is therefore contraindicated [*see Contraindications (4.1), Drug Interactions (7.1), and Clinical Pharmacology (12.2)*].

When sildenafil tablets are co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating sildenafil tablets treatment and sildenafil tablets should be initiated at 25 mg [*see Warnings and Precautions (5.5), Drug Interactions (7.2), and Clinical Pharmacology (12.2)*].

2.4 Dosage Adjustments Due to Drug Interactions

Ritonavir

The recommended dose for ritonavir-treated patients is 25 mg prior to sexual activity and the recommended maximum dose is 25 mg within a 48 hour period because concomitant administration increased the blood levels of sildenafil by 11-fold [*see Warnings and Precautions (5.6), Drug Interactions (7.4), and Clinical Pharmacology (12.3)*].

CYP3A4 Inhibitors

Consider a starting dose of 25 mg in patients treated with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or saquinavir) or erythromycin. Clinical data have shown that co-administration with saquinavir or erythromycin increased plasma levels of sildenafil by about 3 fold [*see Drug Interactions (7.4) and Clinical Pharmacology (12.3)*].

2.5 Dosage Adjustments in Special Populations

Consider a starting dose of 25 mg in patients > 65 years, patients with hepatic impairment (e.g., cirrhosis), and patients with severe renal impairment (creatinine clearance <30 mL/min), concomitant administration of sildenafil tablets in these patients resulted in higher plasma levels of sildenafil [*see Use in Specific Populations (8.5, 8.6, 8.7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Sildenafil tablets, USP are supplied as pale blue to blue, capsel shaped film-coated tablets containing sildenafil citrate USP equivalent to 50 mg, or 100 mg of sildenafil. Tablets are debossed with 1A1 and 1A2 on one side and plain on the other to indicate the dosage strengths viz. 100 mg and 50 mg respectively. Sildenafil tablets 25 mg USP is supplied as Pale blue to blue, round film-coated tablets, debossed with "25" on one side and "SL" on other side.

4 CONTRAINDICATIONS

4.1 Nitrates

Consistent with its known effects on the nitric oxide/cGMP pathway [*see Clinical Pharmacology (12.1, 12.2)*], sildenafil tablets was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using nitric oxide donors such as organic nitrates or organic nitrites in any form either regularly and/or intermittently is therefore contraindicated.

After patients have taken sildenafil tablets, it is unknown when nitrates, if necessary, can be safely administered. 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 co-administered at this time point [*see Dosage and Administration (2.3), Drug Interactions (7.1), and Clinical Pharmacology (12.2)*].

4.2 Hypersensitivity Reactions

Sildenafil tablets are contraindicated in patients with a known hypersensitivity to sildenafil, as contained in sildenafil tablets and REVATIO, or any component of the tablet. Hypersensitivity reactions have been reported, including rash and urticaria [*see Adverse Reactions (6.1)*].

4.3 Concomitant Guanylate Cyclase (GC) Stimulators

Do not use sildenafil tablets in patients who are using a GC stimulator, such as riociguat. PDE5 inhibitors, including sildenafil, may potentiate the hypotensive effects of GC stimulators.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including sildenafil, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Sildenafil has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg) [*see Clinical Pharmacology (12.2)*]. While this response in healthy men would be expected to be of little consequence in most patients, prior to prescribing sildenafil, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Use with caution in patients with the following underlying conditions which can be particularly sensitive to the actions of vasodilators including sildenafil – those with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure.

There are no controlled clinical data on the safety or efficacy of 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 mmHg) or hypertension (BP >170/110 mmHg);
- Patients with cardiac failure or coronary artery disease causing unstable angina.

5.2 Prolonged Erection and Priapism

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of sildenafil tablets. In the event of a prolonged erection lasting longer than 4 hours, the patient should seek medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Sildenafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia). However, there are no controlled clinical data on the safety or efficacy of sildenafil in patients with sickle cell or related anemias.

5.3 Effects on the Eye

Physicians should advise patients to stop use of all phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision including permanent loss of vision, that has been reported rarely post-marketing in temporal association with the use of all PDE5 inhibitors. Physicians should discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye. Physicians should also discuss with patients the increased risk of NAION among the general population in patients with a "crowded" optic disc, although evidence is insufficient to support screening of prospective users of PDE5 inhibitor, including sildenafil, for this uncommon condition [*see Warnings and Precautions (5.3) and Adverse Reactions (6.2)*].

Neither the rare post-marketing reports, nor the association of PDE5 inhibitor use and NAION in the observational studies, substantiate a causal relationship between PDE5 inhibitor use and NAION [*see Adverse Reactions (6.2)*].

Physicians should consider whether their patients with underlying NAION risk factors could be affected adversely by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors, including sildenafil, should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with "crowded" optic discs are also considered at greater risk for NAION compared to the general population, however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including sildenafil, for this uncommon condition.

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.

5.4 Hearing Loss

Physicians should advise patients to stop taking PDE5 inhibitors, including sildenafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including sildenafil. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors [*see Adverse Reactions (6.1, 6.2)*].

5.5 Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives

Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including sildenafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When both vasodilators are taken in combination, an additive effect on blood pressure may occur. In some patients, concomitant use of these two drug classes can lower blood pressure significantly [*see Drug Interactions (7.2) and Clinical Pharmacology (12.2)*] leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant PDE5 inhibitor use. Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor.
- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose [*see Dosage and Administration (2.3)*].
- In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blockers should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.
- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Anti-hypertensives

Sildenafil has systemic vasodilatory properties and may further lower blood pressure in patients taking antihypertensive medications.

In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and sildenafil, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reductions of 8 mmHg systolic and 7 mmHg diastolic were noted [*see Drug Interactions (7.3) and Clinical Pharmacology (12.2)*].

5.6 Adverse Reactions with the Concomitant Use of Ritonavir

The concomitant administration of the protease inhibitor ritonavir substantially increases serum concentrations of sildenafil (11-fold increase in AUC). It sildenafil is prescribed to patients taking ritonavir, caution should be used. Data from subjects exposed to high systemic levels of sildenafil are limited. Decreased blood pressure, syncope, and prolonged erection were reported in some healthy volunteers exposed to high levels of sildenafil (200-800 mg). To decrease the chance of adverse reactions in patients taking ritonavir, a decrease in sildenafil dosage is recommended [*see Dosage and Administration (2.4), Drug Interactions (7.4), and Clinical Pharmacology (12.3)*].

5.7 Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies

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

5.8 Effects on Bleeding

There have been postmarketing reports of bleeding events in patients who have taken sildenafil. A causal relationship between sildenafil and these events has not been established. In humans, sildenafil has no effect on bleeding time when taken alone or with aspirin. However, *in vitro* studies with human platelets indicate that sildenafil potentiates the antihaemostatic effect of sodium nitroprusside (a nitric oxide donor). In addition, 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.

The safety of sildenafil is unknown in patients with bleeding disorders and patients with active peptic ulceration.

5.9 Counseling Patients About Sexually Transmitted Diseases

The use of sildenafil offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labelling:

- Cardiovascular [*see Warnings and Precautions (5.1)*],
- Prolonged Erection and Priapism [*see Warnings and Precautions (5.2)*]
- Effects on the Eye [*see Warnings and Precautions (5.3)*]
- Hearing Loss [*see Warnings and Precautions (5.4)*]
- Hypotension when Co-administered with Alpha-blockers or Anti-hypertensives [*see Warnings and Precautions (5.5)*]
- Adverse Reactions with the Concomitant Use of Ritonavir [*see Warnings and Precautions (5.6)*]
- Combination with other PDE5 Inhibitors or Other Erectile Dysfunction Therapies [*see Warnings and Precautions (5.7)*]
- Effects on Bleeding [*see Warnings and Precautions (5.8)*]
- Counseling Patients About Sexually Transmitted Diseases [*see Warnings and Precautions (5.9)*]

The most common adverse reactions reported in clinical trials (≥2%) are headache, flushing, dyspepsia, abnormal vision, nasal congestion, back pain, myalgia, nausea, dizziness, and rash.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

In placebo-controlled clinical studies, the discontinuation rate due to adverse reactions for sildenafil (2.5%) was not significantly different from placebo (2.3%).

In fixed-dose studies, the incidence of some adverse reactions increased with dose. The type of adverse reactions in flexible-dose studies, which reflected the recommended dosage regimen, was similar to that for fixed-dose studies. At doses above the recommended dose range, adverse reactions were similar to those detailed in Table 1 but generally were reported more frequently.

Table 1: Adverse Reactions Reported by ≥2% of Patients Treated with sildenafil and More Frequent than Placebo in Fixed-Dose Phase II/III Studies

Adverse Reaction	25 mg (n=312)	50 mg (n=511)	100 mg (n=506)	Placebo (n=607)
Headache	16%	21%	28%	7%
Flushing	10%	19%	18%	2%
Dyspepsia	3%	9%	17%	2%
Abnormal vision[a]	2%	2%	11%	1%
Nasal congestion	4%	4%	9%	2%
Back pain	3%	4%	4%	2%
Myalgia	2%	2%	4%	1%
Nausea	2%	3%	3%	1%
Dizziness	3%	4%	3%	2%
Rash	1%	2%	3%	1%

[a]Abnormal Vision: Mild to moderate in severity and transient, predominantly color tinge to vision, but also increased sensitivity to light, or blurred vision.

When sildenafil was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials of two to twenty-six weeks duration, patients took sildenafil at least once weekly, and the following adverse reactions were reported:

Table 2: Adverse Reactions Reported by ≥2% of Patients Treated with sildenafil and More Frequent than Placebo in Flexible-Dose Phase II/III Studies

Adverse Reaction	SILDENAFIL CITRATE N=734	PLACEBO N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Abnormal Vision[a]	3%	0%
Back pain	2%	2%
Dizziness	2%	1%
Rash	2%	1%

[a]Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

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

Body as a Whole: face edema, hypersensitivity reaction, chest, neck, arthralgia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypertension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hyponatremia.

Musculoskeletal: arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: sudden decrease or loss of hearing, mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, ear pain, eye hemorrhage, cataract, dry eyes.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and angioma.

Analysis of the safety database from controlled clinical trials showed no apparent difference in adverse reactions in patients taking sildenafil with and without antihypertensive medication. This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of sildenafil. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion either due to their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors.

Cardiovascular and cerebrovascular

Serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have been reported post-marketing in temporal association with the use of sildenafil. Most, but not all, of these patients had preexisting 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 and 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 a combination of these factors, or to other factors [*see Warnings and Precautions (5.1) and Patient Counseling Information (17)*].

Hemic and Lymphatic: vaso-occlusive crisis: In a small, prematurely terminated study of REVATIO (sildenafil) in patients with pulmonary arterial hypertension (PAH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported in patients who received sildenafil than in those randomized to placebo. The clinical relevance of this finding to men treated with sildenafil for ED is not known.

Nervous: seizure, seizure recurrence, anxiety, and transient global amnesia.

Respiratory: epistaxis

Special Senses:
Hearing: Cases of sudden decrease or loss of hearing have been reported postmarketing 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 reported 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 Warnings and Precautions (5.4) and Patient Counseling Information (17)*].

Eyes: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, and photophobia were commonly reported in patients who received sildenafil than in those randomized to placebo. The clinical relevance of this finding to men treated with sildenafil for ED is not known.

Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported rarely post-marketing in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. [*see Warnings and Precautions (5.3) and Patient Counseling Information (17)*].

Urogenital: prolonged erection, priapism [*see Warnings and Precautions (5.2) and Patient Counseling Information (17)*], and hematuria.

7 DRUG INTERACTIONS

7.1 Nitrates

Administration of sildenafil with nitric oxide donors such as organic nitrates or organic nitrites in any form is contraindicated. Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates [*see Dosage and Administration (2.3), Contraindications (4.1), Clinical Pharmacology (12.2)*].

7.2 Alpha-blockers

Use caution when co-administering alpha-blockers with sildenafil because of potential additive blood pressure- lowering effects. When sildenafil is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment and sildenafil should be initiated at the lowest dose [*see Dosage and Administration (2.3), Warnings and Precautions (5.5), Clinical Pharmacology (12.2)*].

7.3 Amlodipine

When sildenafil 100 mg was co-administered with amlodipine (5 mg or 10 mg) to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic [*see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)*].

7.4 Ritonavir and other CYP3A4 inhibitors

Co-administration of ritonavir, a strong CYP3A4 inhibitor, greatly increased the systemic exposure of sildenafil (11-fold increase in AUC). It is therefore recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48 hour period [*see Dosage and Administration (2.4), Warnings and Precautions (5.6), Clinical Pharmacology (12.3)*].

Co-administration of erythromycin, a moderate CYP3A4 inhibitor, resulted in a 160% and 182% increases in sildenafil C_{max} and AUC, respectively. Co-administration of saquinavir, a strong CYP3A4 inhibitor, resulted in 140% and 210% increases in sildenafil C_{max} and AUC, respectively. Stronger CYP3A4 inhibitors such as ketoconazole or itraconazole could be expected to have greater effects than seen with saquinavir. A starting dose of 25 mg of sildenafil should be considered in patients taking erythromycin or strong CYP3A4 inhibitors (such as saquinavir, ketoconazole, itraconazole) [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].

7.5 Alcohol

In a drug-drug interaction study sildenafil 50 mg given with alcohol (0.5 g/kg in which mean maximum blood alcohol levels of 0.08% was achieved, sildenafil did not potentiate the hypotensive effect of alcohol in healthy volunteers [*see Clinical Pharmacology (12.2)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Sildenafil is not indicated for use in females.

There are no data with the use of sildenafil in pregnant women to inform any drug-associated risks for adverse developmental outcomes. Animal reproduction studies conducted with sildenafil do not show adverse developmental outcomes when administered during organogenesis in rats and rabbits at oral doses up to 16 and 32 times, respectively, the maximum recommended human dose (MRHD) of 100 mg/day on a mg/m² basis (see Data).

Data
Animal Data
No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received oral doses up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 16 and 32 times the MRHD on a mg/m² 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, about 2 times the MRHD on a mg/m² basis in a 50 kg subject.

8.2 Lactation

Risk Summary
Sildenafil is not indicated for use in females.
Limited data indicate that sildenafil and its active metabolite are present in human milk. There is no information on the effects on the breastfed child, or the effects on milk production.

8.4 Pediatric Use

Sildenafil is contraindicated for use in pediatric patients. Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil resulting in approximately 84% and 107% higher plasma AUC values of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy young volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively [*see Dosage and Administration (2.5), and Use in Specific Populations (8.5)*].

Renal Impairment: 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 approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment [*see Dosage and Administration (2.5), and Use in Specific Populations (8.6)*].

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

Hepatic Impairment: In volunteers with hepatic impairment (Child-Pugh Class 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 severely impaired hepatic function (Child-Pugh Class C) have not been studied [*see Dosage and Administration (2.5), and Use in Specific Populations (8.7)*].

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in these patients [*see Dosage and Administration (2.5)*].

Drug Interaction Studies

Effects of Other Drugs on sildenafil

Sildenafil metabolism is principally mediated by CYP3A4 (major route) and CYP2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance. The concomitant use of erythromycin or strong CYP3A4 inhibitors (e.g., saquinavir, ketoconazole, itraconazole) as well as the nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil [*see Dosage and Administration (2.4)*].

***In vivo* studies:**

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

When a single 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 160% increase in sildenafil C_{max} and a 182% increase in sildenafil AUC. In addition, in a study performed in healthy male volunteers, co-administration of the HIV protease inhibitor saquinavir, also a CYP3A4 inhibitor, at steady state (1200 mg tid) 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. A stronger CYP3A4 inhibitor such as ketoconazole or itraconazole could be expected to have greater effect than that seen with saquinavir. Population pharmacokinetic data from patients in clinical trials also indicated a reduction in sildenafil clearance when it was co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine) [*see Dosage and Administration (2.4) and Drug Interactions (7.4)*].

In another study in healthy male volunteers, co-administration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg bid) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil AUC. At 24 hours the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics [*see Dosage and Administration (2.4) and Drug Interactions (7.4)*].

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

In a study of healthy male volunteers, co-administration of sildenafil at steady state (80 mg t.i.d.) with endothelin receptor antagonist bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) at steady state (125 mg b.i.d.) resulted in a 63% decrease of sildenafil AUC and a 50% decrease of sildenafil C_{max}. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma levels of sildenafil.

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

In healthy male volunteers, there was no evidence of a clinically significant effect of azithromycin (500 mg daily for 3 days) on the systemic exposure of sildenafil or its major circulating metabolite.

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, 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.

Effects of sildenafil on Other Drugs

***In vitro* studies:**

Sildenafil is a weak inhibitor of the CYP isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that sildenafil will alter the clearance of substrates of these isoenzymes.

***In vivo* studies:**

No significant interactions were shown with tolbutamide (250