SEDEOGRA

(Sildenafil Citrate Film-Coated Tablets)

1. Product Name and Product Description

SEDEOGRA (50 mg): Blue, diamond-shaped, one side with "SF50" marked and the other side with "GPO" marked, film-coated tablets.

SEDEOGRA (100 mg): Blue, diamond-shaped, one side with "SF100" marked and the other side with "GPO" marked, film-coated tablets.

2. Name and Strength of Active Ingredient

SEDEOGRA (50 mg): Each film-coated tablet contains Sildenafil 50 mg.

SEDEOGRA (100 mg): Each film-coated tablet contains Sildenafil 100 mg.

3. Pharmacodynamics/Pharmacokinetics

3.1 Pharmacodynamics

Erectile dysfunction (ED)

Does not directly cause penile erections, but affects the response to sexual stimulation. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum; when sexual stimulation causes local release of NO, inhibition of PDE-5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum; at recommended doses, it has no effect in the absence of sexual stimulation.

3.2 Pharmacokinetics

Sildenafil pharmacokinetics is dose-proportional over the recommended dose range.

Absorption

Sildenafil is rapidly and almost completely absorbed after oral administration, with mean bioavailability of 40% (range 25-63%). Maximum observed plasma concentrations (T_{max}) are reached within 30 to 120 minutes (mean 60 minutes). 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%.

Distribution

The volume of distribution (Vd) for sildenafil is 105 L. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Metabolism

Sildenafil is cleared predominantly by the CYP3A4 (major) and CYP2C9 (minor) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. The metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolized, with a terminal half-life of approximately 4 hours.

Elimination

Half-life elimination of sildenafil is 4 hours; the elderly and those with severe renal impairment or hepatic function impairment (hepatic cirrhosis (Child Pugh Class A and B) have reduced clearance of sildenafil and its active N-desmethyl metabolite. After either oral administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80%) and to a lesser extent in the urine (approximately 13%).

4. Indication

Used for treatment of erectile dysfunction (ED).

5. Recommended Dose

Adults:

- *Usual dosage:* 50 mg taken as needed, approximately 1 hour before sexual activity. However, sildenafil may be taken anywhere from 30 minutes to 4 hours before sexual activity.
- *Maximum dose:* 100 mg once daily. The maximum recommended dosing frequently is once daily.
- *Dosage adjustment:* May be increased to a maximum recommended dose of 100 mg or decreased to 25 mg, based on efficacy and toleration.

Elderly > 65 years: Use with caution. Starting dose of 25 mg should be considered.

Dosage considerations for patients stable on alpha-blockers: Initial 25 mg.

Dosage adjustment for concomitant use of potent CYP3A4 inhibitors:

Erythromycin, itraconazole, ketoconazole, saquinavir: Starting dose of 25 mg for sildenafil should be considered.

Ritonavir: Not to exceed a maximum single dose of sildenafil 25 mg in a 48-hour period.

Dosage adjustment in renal impairment:

Cl_{cr} < 30 mL/minute: Starting dose of 25 mg should be considered

Dosage adjustment in hepatic impairment:

Starting dose of 25 mg should be considered; not studied in severe impairment (Child-Pugh class C).

6. Mode of Administration

Administer orally approximately 1 hour before sexual activity (may be used anytime from 30 minutes to 4 hours before). Note: The tablet cannot split and should be taken as whole

7. Contraindications

Sildenafil is contraindicated in patients with known hypersensitivity to sildenafil or any component of the formulation; concurrent use (regularly/intermittently) of organic nitrates in any form (e.g., nitroglycerin, isosorbide dinitrate).

8. Warnings and Precautions

Concerns related to adverse effects:

- *Visual disturbances:* May cause dose-related impairment of color discrimination (blue/ green). Use is not recommended in patients with retinitis pigmentosa. A minority of retinitis pigmentosa have genetic disorders of retinal phosphodiesterases (no safety information available).
- *Hearing loss:* Sudden decrease or loss of hearing has been reported rarely; hearing changes may be accompanied by tinnitus and dizziness. A direct relationship between therapy and hearing loss has not been determined.
- *Hypotension:* Decreases in blood pressure may occur due to vasodilator effects; use with caution in patients with left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy); may be more sensitive to hypotensive actions.

Concurrent use with alpha-adrenergic antagonist therapy or substantial alcohol consumption may cause symptomatic hypotension; patients should be hemodynamically stable prior to initiating therapy at the lowest possible dose.

- *Vision loss:* Vision loss may occur rarely and be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). Risk may be increased with history of vision loss. Other risk factors for NAION include low cup-to-disc ratio ("crowded disc"), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and > 50 years of age.
- *Priapism and prolonged erection:* Painful erection > 6 hours in duration; rare. Educate patient to seek medical assistance for erection lasting > 4 hours.

Disease-related concerns :

- Anatomical penis deformation: Use with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease).
- Bleeding disorders: Use with caution in patients with bleeding disorders; safety and efficacy have not been established. *In vitro* studies have suggested a decreased effect on platelet aggregation.
- *Cardiovascular disease:* Use with caution in patients with hypotension (< 90/50 mm Hg); uncontrolled hypertension (> 170/110 mm Hg); life-threatening arrhythmias, stroke or myocardial infarction within the last 6 months; cardiac failure or coronary artery disease causing unstable angina; safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (e.g., aortic stenosis). There is a degree of cardiac risk associated with sexual activity; therefore, physicians should consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.
- *Conditions predisposing to priapism:* Use with caution in patients who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia). All patients should be instructed to seek immediate medical attention if erection persists > 4 hours.
- *Hepatic impairment:* Use with caution in patients with hepatic impairment; use lowest starting dose (25 mg).
- *Peptic ulcer disease:* Use with caution in patients with active peptic ulcer disease; safety and efficacy have not been established.
- *Renal impairment:* Use with caution in patients with renal impairment; dose adjustment may be needed; use lowest starting dose (25 mg) in severe dysfunction (Cl_{cr} < 30 mL/minute).

Concurrent drug therapy issues:

- *Alpha-blockers:* Use with caution in patients taking alpha-blockers; may cause symptomatic hypotension. Initiate sildenafil at the lowest recommended dose. Alpha-blockers should be initiated at the lowest recommended dose in patients currently receiving sildenafil.
- *High potential for interactions:* Use with caution in patients taking strong CYP3A4 inhibitors (e.g., ritonavir can increase sildenafil levels, initiate sildenafil at decreased dose); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.
- *Nitrates:* Concomitant (regularly/intermittently) use with all forms of nitrates is contraindicated. If nitrate administration is medically necessary, it is not known when nitrates can be safely administered following the use of sildenafil; the American College of Cardiology/ American Heart Association (ACC/AHA) 2007 guidelines supports administration of nitrates only if 24 hours have elapsed.
- *Other treatments for erectile dysfunction:* Safety and efficacy with other treatments for erectile dysfunction have not been established; use is not recommended.

Elderly

Use with caution; dose adjustment may be required.

Since the elderly often have concomitant diseases, many of which may contraindicate the use of sildenafil, a thorough knowledge of diseases and medications used must be assessed. Adjust dose for renal/hepatic function.

9. Interactions with Other Medicaments

Effects of other medicinal products on sildenafil

In vitro studies:

Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minorroute). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

In vivo studies:

Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildanafil clearance when co administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine)

Cimetidine (800 mg), a cytochrome P450 inhibitor and a nonspecific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with sildenafil (50 mg) to healthy volunteers.

When a single 100 mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In addition, coadministration 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 Cmax and a 210% increase in sildenafil AUC. Sildenafil had no effect on saquinavir pharmacokinetics. Stronger CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have greater effects.

Coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics.

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. Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of 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, ACE inhibitors, and calcium channel blockers.

In normal healthy male volunteer, 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 major circulating metabolite.

Effects of sildenafil on other medicinal products

In vitro studies:

Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (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:

Sildenafil was shown to potentiate the hypotensive effect of acute and chronic nitrates. Therefore, use of nitric oxide donors, organic nitrites in any form either regularly or intermittently with sildenafil is contraindicated.

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, and 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals.

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

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

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

Sildenafil (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%(80 mg/dL).

No interaction was seen when sildenafil (100 mg) was coadministered with amlodipine in hypertensive patients. The mean additional reduction on supine blood pressure was 8 mmHg systolic and 7mmHg diastolic.

Analysis of the safety database showed no difference in the side effect profile in patient taking sildenafil with and without antihypertensive medication.

10. Pregnancy and Lactation

Pregnancy

Pregnancy category B

Teratogenic effects were not observed in animal studies. There are no adequate and well-controlled studies in pregnant women.

Lactation

Excretion in breast milk unknown/use caution

11. Undesirable Effects

Cardiovascular :	Flushing (10%), angina pectoris, chest pain, hypotension, palpitation, postural hypotension, syncope, tachycardia (< 2%), abnormal electrocardiogram, atrioventricular (AV) block, cardiac arrest, cardiomyopathy, cerebral thrombosis, heart failure, myocardial ischemia, hypertension
Central nervous system :	Headache (46%), insomnia (7%), paresthesia (3%), dizziness (2%), abnormal dreams, ataxia, decreased reflexes, depression, hypertonia, hyperesthesia, migraine, neuralgia, neuropathy, tremor, vertigo (< 2%) Postmarketing : anxiety, seizure
Dermatologic :	Erythema (6%), rash (2%), contact dermatitis, exfoliative dermatitis, photosensitivity, herpes simplex, pruritus, skin ulcer, sweating, urticaria (< 2%)
EENT (Ear, eye, nose, and throat system) :	Epistaxis (9%), nasal congestion, rhinitis (4%), abnormal vision (3%), cataract, conjunctivitis, dry eyes, ear pain, eye hemorrhage, eye pain, mydriasis, photophobia, sudden decrease or loss of hearing, tinnitus (< 2%) Postmarketing: diplopia, increased intraocular pressure, ocular burning, ocular redness, ocular swelling, retinal vascular disease, temporary vision loss/ decreased vision, vitreous detachment
Gastrointestinal :	Dyspepsia (17%), diarrhea (9%), gastritis (3%), colitis, dry mouth, dysphagia, esophagitis, gastroenteritis, gingivitis, glossitis, rectal hemorrhage, stomatitis, vomiting (< 2%), abnormal liver function tests (< 2%)
Genitourinary :	Urinary tract infection (3%), abnormal ejaculation, anorgasmia, breast entargement, cystitis, genital edema, nocturia, urinary frequency, urinary incontinence (< 2%), hematuria, priapism
Hematologic :	Anemia, leukopenia (< 2%)
Metabolic :	Edema, gout, hyperglycemia, hypernatremia, hyperuricemia, hypoglycemic reaction, peripheral edema, thirst, unstable diabetes
Musculoskeletal :	Myalgia (7%), arthritis, arthrosis, bone pain, myasthenia, synovitis, tendon rupture, tenosynovitis
Respiratory :	Dyspnea exacerbated (7%), sinusitis (3%), asthma, bronchitis, increased cough, increased sputum, laryngitis, pharyngitis (< 2%)
Miscellaneous :	Pyrexia (6%), allergic reaction, asthenia, chills, face edema, pain, shock, anaphylactic reaction

12. Overdose and Treatment

Manifestation

In studies with healthy volunteers of single sildenafil doses up to 800 mg, adverse reactions were similar to those seen at lowerdoses, but incidence rates were increased.

Treatment

In cases of overdose, adopt standard supportive measures as required. Renal dialysis is not expected to accelerate clearance as these drugs are highly bound to plasma proteins and are not significantly eliminated in urine.

13. List of Excipients

Microcrystalline Cellulose PH101
Croscarmellose Sodium (type A)
Polyvinyl pyrrolidone K30
Purified water
Microcrystalline Cellulose PH102
Sodium Starch Glycolate
Colloidal Silicon Dioxide
Magnesium Stearate
Opadry Blue OY-30021
Opadry Clear YS-1-7006

14. Storage condition

Store below 30°C and protect from light

15. Dosage Form and Packaging Available

Box of 4 film-coated tablets

16. Name and Address of Manufacturing

The Government Pharmaceutical Organization
Main Office : 75/1 Rama VI Rd., Ratchathewi, Bangkok, Thailand
Manufacturer : 138 Moo 4, Rangsit-Nakhonnayok Rd., Bueng Sanan, Thanyaburi, Pathumthani, Thailand

17. Date of Revision of Package Insert

August 2012