SILDENAFIL CITRATE

ANDROS®

25 mg, 50 mg, 100 mg Film-coated Tablet
Selective phosphodiesterase-5 (PDE5) inhibitor

FORMULATION
Each film-coated tablet contains:
Sildenafil (as citrate) ……..…… 25 mg, 50 mg, 100 mg

PRODUCT DESCRIPTIONS
Sildenafil (Andros 25 mg) is a blue, elliptical-shaped, 0.1622" x 0.4012" plain, film-coated tablet
Sildenafil (Andros 50 mg) is a blue, oval-shaped, 0.291" x 0.474", plain on both sides, film-coated tablet.
Sildenafil (Andros 100 mg) is a blue, elliptical-shaped, 0.300" x 0.662", bisected on one side and plain on the other side, film-coated tablet

CLINICAL PHARMACOLOGY
Pharmacodynamics
Sildenafil is a selective inhibitor of phosphodiesterases (PDEs). It has greatest selectivity for PDE type 5 (PDE5), an isoenzyme that inactivates cyclic guanosine monophosphate (cGMP). PDE5 is the predominant type in the corpus cavernosum of the penis and is involved in the breakdown (hydrolysis) of cGMP to GMP.

Nitric oxide (NO) released in the corpus cavernosum during sexual stimulation is most likely the major neurotransmitter mediating physiologic penile erection. NO mediates relaxation of the vascular smooth muscle of the corpus cavernosum by activating soluble guanylate cyclase thereby increasing cGMP production. cGMP is a second messenger for G-protein-coupled receptor protein kinases involved in regulating the vascular tone of the arterioles of the corpus cavernosum.

Sildenafil enhances penile erection by augmenting NO-mediated, cGMP-dependent vascular smooth muscle relaxation pathways. Upon NO release during sexual stimulation (resulting in increased cGMP production), Sildenafil (by inhibiting cGMP breakdown thus increasing cGMP levels in the corpus cavernosum) produces smooth muscle relaxation of the corpus cavernosum. Vascular smooth muscle relaxation in the corpus cavernosum leads to increased penile blood flow. Sildenafil has no effect on penile erection in the absence of sexual arousal.

Pharmacokinetics
Sildenafil is readily absorbed with peak plasma concentrations achieved approximately 60 minutes after oral administration in the fasted state. Sildenafil undergoes extensive metabolism in the GI mucosa during absorption and on first pass through the liver. Hence, sildenafil's mean absolute oral bioavailability is only about 41%. Taking sildenafil with food, particularly with a high fat meal, delays absorption and decreases maximum plasma sildenafil concentration possibly due to delayed gastric emptying.

Sildenafil is about 96% bound to plasma protein and its mean apparent steady state volume of distribution is approximately 105 L.

Sildenafil is primarily metabolized in the liver through the hepatic cytochrome P450 (CYP450) enzymes 3A4 and 2C9 and excreted mainly as metabolites mainly in the feces and to a lesser extent in the urine. The active N-desmethyl metabolite is reported to account for about 20% of sildenafil's pharmacologic activity and reach plasma concentrations that are about 40% of those seen with sildenafil.

Sildenafil's apparent terminal half-life ranges from 3 to 5 hours over the dose range of 25 mg and 200 mg. This allows an appropriate duration of therapeutic effect while preventing accumulation of the drug with chronic once-daily dosing.

Old age (65 years and older) increases sildenafil and N-desmethyl metabolite (active metabolite) plasma levels by about 90% compared to those seen in younger volunteers (18 - 45 years old) due to reduced clearance of sildenafil. The corresponding increase in free sildenafil plasma concentration was approximately 40% due to the age-differences in plasma protein binding.

Compared with patients with no hepatic impairments, sildenafil clearance was reduced in patients with hepatic impairment (Child-Pugh A and B). Sildenafil has not been studied in patients with severe hepatic impairment (Child-Pugh C).

Increased sildenafil levels were observed in patients with severe renal impairment (Cl_{cr} ≤ 30 mL/min). However, sildenafil pharmacokinetics was not altered in patients with mild (Cl_{cr} = 50-80 mL/min) to moderate (Cl_{cr} 30-49 mL/min) renal impairment.

INDICATION
· For the treatment of erectile dysfunction

DOSAGE AND ADMINISTRATION
Usual Recommended Oral Dose: 50 mg taken, as needed, approximately one hour before sexual activity
Sildenafil may be taken anywhere from 4 hours to 30 minutes before sexual activity.

Sildenafil dose may be increased to the maximum recommended oral dose of 100 mg or decreased to 25 mg based on patient response and tolerance.

***Maximum Recommended Dose*:** 100 mg
***Maximum Recommended Dosing Frequency*:** Once a day

Sildenafil plasma levels are increased in patients with the following conditions:
· Age >65 years
· Severe liver impairment (e.g., cirrhosis)
· Severe kidney impairment (creatinine clearance < 30 mL/min)
· Concomitant use of potent cytochrome P450, 3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, saquinavir)

A starting dose of 25 mg should be considered in these patients.

Make sure that patients who are taking alpha-blockers concomitantly with sildenafil are stable on alpha-blocker therapy before starting treatment with sildenafil. Initiate sildenafil at the lowest possible dose in these patients.

CONTRAINDICATIONS
- Known hypersensitivity to sildenafil or to any ingredient in this product
- Patients who are using any form of organic nitrates, nitrites, nitric oxide donors (e.g., sodium nitroprusside) either regularly and/or intermittently since severe, potentially fatal hypotensive episodes can occur
- Patients in whom sexual activity is inadvisable (e.g., patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure)
- Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION) regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see **Warnings and Precautions**)

WARNINGS AND PRECAUTIONS
Patients should be diagnosed (i.e., medical history and physical examination) for erectile dysfunction and potential underlying causes determined before starting treatment with sildenafil.
There are no controlled clinical studies on the safety and efficacy of sildenafil in the following sub-groups of patients, and if prescribed, should be done with caution:
- Recent (within the last 6 months) myocardial infarction, stroke or life-threatening arrhythmia
- Resting hypotension (<90/50 mmHg) or hypertension (>170/110 mmHg)
- Severe hepatic impairment
- Severe renal impairment
- Known hereditary degenerative retinal disorders such as retinitis pigmentosa
- Sickle cell anemia or related anemias

Cardiovascular
Sexual activity in men with cardiovascular disease is associated with cardiac risks such as increase in cardiac work, heart rate, blood pressure, and myocardial oxygen demand similarly produced with moderate exercise. Thus, assessment of cardiovascular and cerebrovascular status of patients is necessary before initiating any treatment for erectile dysfunction. Erectile dysfunction treatments are generally not recommended when sexual activity is inadvisable due to the patient's underlying cardiovascular status. Advice patients to refrain from further sexual activity when they experience related symptoms like angina pectoris, dizziness or nausea upon initiation of sexual activity.

Some patients, particularly those with underlying cardiovascular disease, may be adversely affected by sildenafil's vasodilatory activity, especially in combination with sexual activity. Inform patients of the risk of hypotension especially when patients are on multidrug regimen for hypertension. Patients with increased susceptibility to vasodilators include those with:
- Left ventricular outflow obstruction (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy)
- Rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure

Use phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil, with caution when given together with alpha-blockers. Sildenafil, other PDE5 inhibitors, and alpha-adrenergic blocking agents are vasodilators and an additive hypotensive effect may be anticipated. Concurrent use of these drug classes can lead to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting) in some patients. Consider the following before using sildenafil concurrently with alpha-blockers:
- Make sure that patients are stable on alpha-blocker therapy before starting sildenafil or other PDE5 inhibitors.
- Initiate PDE5 inhibitors at the lowest dose in patients who are stable on alpha-blocker therapy.
- In patients already taking a PDE5 inhibitor at the optimized dose, initiate alpha-blocker therapy at the lowest dose. When taking a PDE5 inhibitor, further lowering of blood pressure may result from stepwise increase in alpha-blocker dose.
- Other factors, including intravascular volume depletion and other anti-hypertensive drugs may affect the safety of combined use of PDE5 inhibitors and alpha-blockers.

Hematologic
There is no information on the safety of sildenafil in patients with bleeding disorders or active peptic ulceration. Use sildenafil with caution in these patients.

Genitourinary
Use sildenafil with caution in patients with penile anatomical deformities that may make erections and/or sexual intercourse painful or difficult: e.g., angulation, Peyronie's disease (induration of the penile corpora cavernosa producing a fibrous chordee)

Sildenafil should be used with caution in patients with conditions that may predispose to priapism (painful erection exceeding 6 hours): e.g., sickle-cell anemia, multiple myeloma, leukemia

Prolonged erections and priapism may occur with sildenafil use. Advise patients to seek immediate medical attention if an erection persists longer than 4 hours or is extremely painful. Priapism may lead to penile tissue damage and permanent loss of potency if not treated immediately.

There is no data on the safety and efficacy of sildenafil when used in combination with other agents for the treatment of erectile dysfunction and therefore is not recommended.

Ophthalmologic
Visual disturbances such as changes in blue/green color discrimination may occur in patients taking sildenafil, particularly at high doses. Do not exceed recommended dose and frequency.

Use sildenafil with caution in patients with retinitis pigmentosa (a retinal disorder which in some patients may be accompanied by a genetic disorder of retinal phosphodiesterases).

Immediately stop sildenafil use and seek medical attention when sudden loss of vision in one or both eyes is experienced as this may be a sign of non-arteritic ischemic optic neuropathy (NAION) which may result in decreased vision or permanent vision loss. NAION has been reported rarely with the use of all PDE5 inhibitors although it cannot be determined whether it is directly associated with such drugs or to other factors. The risk of NAION may be higher in patients who:
- Have low cup to disc ratio ("crowded disc")
- Are over 50 years old
- Have diabetes
- Are hypertensive
- Have coronary artery disease
- Have hyperlipidemia
- Smoke

Sudden Decrease or Loss of Hearing
Stop taking PDE5 inhibitors, including sildenafil, and promptly seek medical attention when sudden decrease or loss of hearing occurs. Sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been temporally associated with PDE5 inhibitors, including sildenafil. Whether these events are related directly to PDE5 inhibitors, or to other factors, have not been determined.

Ability to Drive or Operate Machines
Sildenafil may cause visual abnormalities and dizziness. Patients receiving sildenafil should be advised to take precautions while performing activities requiring mental alertness or physical coordination. It should be carefully considered whether it is advisable to drive or operate machinery under these circumstances.

INTERACTIONS WITH OTHER MEDICAMENTS

Drugs Affecting Hepatic Microsomal Enzymes: Since sildenafil is metabolized via the hepatic cytochrome P450 (CYP450) enzymes 3A4 and 2C9, taking sildenafil with the following drugs which inhibit CYP may reduce sildenafil clearance and increase its plasma levels:
- CYP 3A4 and CYP2C9 inhibitors e.g., ritonavir (co-administration is not advised)
- Nonspecific CYP inhibitors, e.g., cimetidine
- Specific CYP3A4 inhibitors, e.g., erythromycin and saquinavir
- Stronger CYP3A4 inhibitors, e.g., ketoconazole or itraconazole
- Weak inhibitors of CYP3A4, e.g., grapefruit juice

On the other hand, CYP3A4 inducers such as rifampicin may decrease plasma sildenafil levels.
Co-administration of sildenafil 80 mg thrice a day (at steady state) and bosentan (moderate inducer of CYP3A4, CYP2C9, and possibly of cytochrome P450 2C19) 125 mg twice a day (at steady state) reduces the area under the concentration-time curve (AUC) and maximum plasma concentration (Cmax) of sildenafil and increases the AUC and Cmax of bosentan.
A starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.
Sildenafil has been shown to have no effect on the pharmacokinetics of tolbutamide and warfarin (CYP2C9 inhibitors) and the selective serotonin reuptake inhibitors and tricyclic antidepressants (CYP2D6 inhibitors).

Alpha-adrenergic Blockers: Concomitant administration of PDE5 inhibitors, including sildenafil, and alpha-adrenergic blockers (e.g., doxazosin, alfuzosin, prazosin, tamsulosin) can significantly lower blood pressure and lead to symptomatic hypotension. (see ***Warnings and Precautions***)

Antihypertensive Agents: The risk of hypotension may be increased in patients taking sildenafil together with antihypertensive therapy and a CYP3A4 inhibitor.
Sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor) *in vitro*.
N-desmethyl sildenafil's AUC was increased by loop and potassium-sparing diuretics (62%) and non-specific beta blockers (102%). These effects on the metabolite are not expected to be of clinical significance.
Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component, it has the potential to have some serious interaction with sildenafil.
No effect on sildenafil pharmacokinetics have been observed when sildenafil is used with thiazide and related diuretics, angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers.

Alcohol: Use of sildenafil 50 mg did not potentiate the hypotensive effect of alcohol in healthy individuals.

Anti-Thrombotic Agents: Sildenafil is not expected to potentiate aspirin-induced increase in bleeding time.

Antacids: Administration with single doses of aluminum- and magnesium hydroxide-containing antacids is not expected to affect the oral bioavailability of sildenafil.

Azithromycin: No effects on the AUC, Cmax, Tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite were observed when used concomitantly with azithromycin.

Other Therapies for Erectile Dysfunction: Combined use of sildenafil with other agents for erectile dysfunction is not recommended. (see **Warnings and Precautions**)
Concomitant use of sildenafil and heparin has been shown to have an additive effect on bleeding time in anesthesized rabbits; however, this interaction has not been studied in humans

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy and Lactation: *Pregnancy Category B*
Sildenafil is not labeled for use in women. No adequate and well-controlled studies have been done using sildenafil in pregnant or breastfeeding women.
Infants and Children: The efficacy and safety of sildenafil in patients younger than 18 years old have not been established. Sildenafil is not indicated for use in neonates and children.

UNDESIRABLE EFFECTS

Sildenafil is generally well-tolerated and its common adverse effects are mild to moderate and generally transient.

Cardiovascular and Cerebrovascular: Angina pectoris, AV block, cardiac arrest, heart failure, myocardial ischemia, atrial fibrillation, unstable angina, tachycardia, palpitation, increased heart rate, hypotension, postural hypotension, syncope, abnormal electrocardiogram, cardiomyopathy, cerebral thrombosis, cerebrovascular accident, and migraine.
Myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, subarachnoid and intracerebral hemorrhages, and pulmonary hemorrhage have also been reported with sildenafil use, mostly in patients with preexisting cardiovascular risk factors.

Gastrointestinal: Vomiting, nausea, glossitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, abnormal liver function tests, rectal hemorrhage, gingivitis, colitis, dyspepsia, diarrhea

Hematologic and Lymphatic: Anemia and leukopenia, vaso-occlusive crisis requiring hospitalization, flushing

Metabolic and Nutritional: Thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, and hypernatremia.

Musculoskeletal: Arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis, arthralgia

CNS: Headache, ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, anxiety, insomnia, somnolence, abnormal dreams, transient global amnesia, decreased reflexes, hypesthesia, dizziness, seizures, and seizure recurrence

Respiratory: Asthma, bronchitis, dyspnea, laryngitis, pharyngitis, sinusitis, increase in sputum and cough, nasal congestion, respiratory tract infection, epistaxis

Skin and Appendages: Urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, and exfoliative dermatitis, rash, Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)

Special Senses: Sudden decrease or loss of hearing (see ***WARNINGS AND PRECAUTIONS***), tinnitus, ear pain, deafness, mydriasis, conjunctivitis, photophobia, eye pain, eye hemorrhage, cataract, dry eyes, abnormal vision (characterized to be mild and transient such as color tinge to vision, blurred vision and increased sensitivity to light), diplopia, temporary vision loss or decreased vision, ocular redness or bloodshot appearance, lacrimation disorders, ocular burning, ocular swelling or pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment or traction, paramacular edema and epistaxis, non-arteritic ischemic optic neuropathy (NAION), resulting in decreased vision and/or permanent vision loss has also been reported. (see ***WARNINGS AND PRECAUTIONS***)

Urogenital: Cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema, anorgasmia, urinary tract infection, prolonged erection, priapism, and hematuria

Immune System Disorders: Hypersensitivity reactions

Body as a Whole: Face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury, flu syndrome, fatigue

OVERDOSAGE AND MANAGEMENT
Limited data is currently available on acute overdosage with sildenafil. Single oral doses of up to 800 mg in healthy volunteers have been shown to have similar adverse events to those seen at lower doses. However, incidence rates and severities were increased in these patients.
Sildenafil overdosage is generally expected to result in extensions of the common adverse reactions to the drug. Increased efficacy was not found with 200 mg dose. However, the incidence of adverse reactions such as headache, flushing, dizziness, dyspepsia, nasal congestion, and altered vision was increased.
Manage sildenafil overdosage with standard supportive measures and therapy.
Since sildenafil is highly bound to plasma proteins and renal clearance is not the major elimination pathway, renal dialysis is not expected to enhance sildenafil clearance in case of overdosage.

STORAGE: Store at temperatures not exceeding 30°C.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY:
Andros® 25 mg film-coated tablet: Polycard of 1's in blister foil (Box of 5's)
Andros® 50 mg film-coated tablet: Polycard of 1's in blister foil (Box of 5's)
Andros® 100 mg film-coated tablet: Polycard of 1's in blister foil (Box of 5's)

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
For UNILAB, Inc.
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

Date of First Authorization:
DR-XY31057 - Andros 25mg film-coated tablet: 9 July 2008
DRP-3050 - Andros 50mg film-coated tablet: 15 June 2011
DRP-3051 - Andros 100mg film-coated tablet: 15 June 2011

P300000021602
Revision Date : June 2018
Reg. IPOPHIL

Trusted Quality Healthcare