Dar Al Dawa

APHRODIL®

(Sildenafil Citrate)

Description:
Aphrodil® (sildenafil citrate), an oral therapy for the treatment of erectile dysfunction; It is a selective competitive inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5).

Clinical pharmacology:
Mechanism of action: The mechanism of penile erection involves the release of nitric oxide (NO) in the corpus cavernosum during the sexual stimulation. (NO) 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 corpus cavernosum, but enhances the nitric oxide (NO) activity by inhibiting phosphodiesterase type 5, which is responsible for degradation of (cGMP) in the corpus cavernosum. Inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of the blood to the corpus cavernosum.
Sildenafil is rapidly absorbed from GI. Maximum observed plasma concentrations are reached within 30 to 120 minutes, after oral dose in fasting state.The rate of absorption is reduced if taken with high fat meal, with a mean delay in T-max of 60 minutes and a mean reduction in C-max of 29%.
Sildenafil and its major circulating N-desmethyl metabolite are 96% bound to plasma proteins. Sildenafil is cleared predominantly by the Cytochrome P450-3A4. It is converted into an active metabolite by N-desmethylation. This active metabolite has a PDE selectivity profile similar to sildenafil. Plasma concentration of this metabolite accounts for 20% of sildenafils' pharmacological effects. Both sildenafil and its metabolite have terminal half-lives of 4 hours.
Sildenafil is excreted as metabolites mainly in the feces (80%) and to a lesser extent in the urine (13%).

Indication:
Aphrodil® is indicated for the treatment of erectile dysfunction.

Contraindications:
Aphrodil® is contraindicated in patients with known hypersensitivity to any component of the tablet. Consistent with its known effects on the nitric oxide/cGMP pathway (see Clinical Pharmacology), sildenafil citrate was shown to potentiate the hypotensive effects of nitrates, and so the administration of Aphrodil to patients who are using organic nitrates, either regulary and/or intermittenly in any form is contraindicated.

Side Effects:
Sildenafil citrate was administered to over 3700 patients (aged 19-87 years) during clinical trails worldwide. Over 550 patients were treated for longer than one year.
In placebo-controlled clinical studies the discontinuation rate due to adverse events for sildenafil citrate (2.5%) was not significantly different from placebo (2.3%).
The adverse events were generally transient and mild to moderate in nature.
In trials of all designs, adverse events reported by patients receiving sildenafil citrate were generally similar.
In fixed -dose studies, the incidence of some adverse events increased with dose, the nature of the adverse events in flexible-doses studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-doses studies.
Adverse events reported by > 2% of patients treated with sildenafil citrate and more frequent on drug than placebo in PRN flexible-dose phase II/III studies.

Adverse Event	Percentage of Patients Reporting Event	
	sildenafil citrate N=734	Placebo N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal congestion	4%	2%
Urinary tract infection	3%	2%
Abnormal vision*	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

* **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.
Other adverse reactions occurred at a rate of > 2%, but equally common on placebo : respiratory tract infection, back pain, flu syndrome, and arthralgia.
In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.
The following events occurred in (<2%) of patients in controlled clinical trials; a causal relationship to sildenafil citrate is uncertain. Reported events include those with a plausible relation to drug use.
Body as a whole: face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.
Cardiovascular: angina pectoris, AV block, migraine, syncope, tachycardia, palpitation,hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.
Digestive: vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, abnormal liver function tests, rectal hemorrhage, gingivitis.
Hemic and lymphatic: anemia and leukopenia.
Metabolic and nutritional: thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperurecemia, hypoglycemic reaction, hypernatremia.
Musculoskeletal: Arthritis, arthrosis, myalgia, tendon rupture tenosynovitis, bone pain, myasthenia and 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: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, catarract, dry eyes.
Urogenital: cystitis, nocturia, unrinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

Warnings:
There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including **Aphrodil®**, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.
Sildenafil citrate 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), While this normally would be expected to be of little consequence in most patients, prior to prescribing Aphrodil, 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.
There is no controlled clinical data on the safety or efficacy of sildenafil citrate in the following groups; if prescribed, this should be done with caution :
* Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
* Patients with resting hypotension (BP < 90/50) or hypertension (BP >170/110);
* Patients with cardiac failure or coronary artery disease causing unstable angina;
* Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

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 citrate. In the event of an erection that persists longer than 4 hours, the patients should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Precautions:
- A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.
- There is a degree of cardiac risk associated with sexual activity; therefore, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.
- Agents for the treatment of erectile dysfunction should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).
- The safety and efficacy of combinations of sildenafil citrate with other treatment for erectile dysfunction have not been studied, therefore, the use of such combination is not recommended.
- Sildenafil citrate has no effect on bleeding time when taken alone or with aspirin. In vitro studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). There is no safety information on the administration of sildenafil citrate to patients with bleeding disorders or active peptic ulceration. Therefore, Aphrodil should be administered with caution to these patients.
- A minority of patients with the inherited condition retinitis pigmentosa have genetic disorders of retinal phosphodiesterases.

There is no safety information on the administration of sildenafil citrate to patients with retinitis pigmentosa. Therefore, Aphrodil should be administered with caution to these patients.
- **Pregnancy:** there are no adequate and well-controlled studies of sildenafil in pregnant women.
- **Lactation:** sildenafil is not indicated for use in lactating women.
- **POST- MARKETING EXPERIENCE:** Physicians should advise patients to stop use of all PDE5 inhibitors, including, Sildenafil citrate and seek medical attention in the event of 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 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. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors.

Drug interactions: Sildenafil metabolism is primarily mediated by the cytochrome P450, therefore, inhibitors of these isoenzymes may reduce sildenafil clearance. Strong cytochrome P3A4 inhibitors such as erythromycin ketoconazole, itraconazole or mibefradil would be expected to increase sildenafil plasma levels.
Information for patients: Physicians should discuss with patients the contraindication of Aphrodil with regular and/or intermittent use of organic nitrates.
Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors.
Patients who experience symptoms (e.g, angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.
physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of sildenafil citrate. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.
The use of **Aphrodil®** offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the human Virus (HIV), may be considered.
Dosage: The recommended dose is 50 mg to be taken 1 hour before sexual activity. The dose may be increased to a maximun recommended dose of 100 mg or decreased to 25 mg.the maximum dosing frequency is once per day.
Dosage adjustment: The following factors are associated with increased plasma levels of sildenafil: Age more than 65 years old, hepatic impairment, renal impairment and concomitant use of potent cytochrome P450-3A4 inhibitors.
These factors may increase the efficacy and incidence of adverse events, therefore, consider the starting dose of 25 mg in these patients.
Overdosage: In case of overdosage supported measures should be instituted. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in urine.
Presentations: **Aphrodil®** 50 Film Coated Tablets. Packs of 4 tablets, 1 tablet. Each tablet contains 50 mg Sildenafil (as Sildenafil Citrate).
Storage condition: Store between 15 - 30°C.

Rx only.

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and it's consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, it's benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you .
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

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Manufactured by Dar Al Dawa , Na'ur - Jordan