Axcel®

SILDENAFIL - 100mg

TABLETS

MAL14085055AZ

COMPOSITION:
Each tablet contains
Sildenafil Citrate
equivalent to Sildenafil 100mg

PRESENTATION:
Blue, biconvex heart-shaped, 12.5 mm x 11.1mm, coated tablet with " KOTRA " embossed on one side and plain on other side.

INDICATIONS:
Sildenafil is indicated for the treatment of erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance. In order for sildenafil to be effective, sexual stimulation is required.

PHARMACOLOGY:
Sildenafil, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Mechanism of Action:
The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during 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 nitric oxide (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 PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and 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 is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1>700-fold for PDE2, PDE3 and PDE4, PDE7-PDE11). The approximately 4000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in the control of cardiac contractility.

Pharmacokinetics:
Sildenafil pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent sidenafil.

Absorption:
Sildenafil is rapidly absorbed after oral administration, with mean absolute bioavailability of 41% (range 25-63%). Sildenafil inhibits the human PDE5 enzyme in vitro by 50% at a concentration of 3.5nM. In man, the mean maximum free plasma concentration of sildenafil following a single oral dose of 100mg is approximately 18ng/ml, or 38nM. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.
When sildenafil is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29%, however, the extent of absorption was not significantly affected (AUC decreased by 11%).

Distribution:
The mean steady state volume of distribution (Vss) for sildenafil is 105L, 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.

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, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. The terminal half-lives of sildenafil and the N-desmethyl metabolite are about 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 faeces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of administered oral dose). Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

DOSAGE AND ADMINISTRATION:
For oral administration only.

Use in adults:
For most patients, the recommended dose is 50mg taken, as needed, approximately 1 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100mg or decreased to 25mg. The maximum recommended daily dose is 100mg. The maximum recommended dosing frequency is once a day.

Use in patients with impaired renal function:
Dosage adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance = 30-80ml/min). Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30ml/min), a 25mg dose should be considered.

Use in patients with impaired hepatic function:
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis), a 25mg dose should be considered.

Use in patients using other medications:
Given the extent of the interaction with patients receiving concomitant therapy with ritonavir (*see DRUG INTERACTIONS*), it is recommended not to exceed a maximum single dose of 25mg of sildenafil in a 48-hours period. A starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP 3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole and itraconazole) (*see DRUG INTERACTIONS*). In order to minimize the potential for developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at lower doses should be considered (*see PRECAUTIONS and DRUG INTERACTIONS*).

Use in children:
Sildenafil is not indicated for use in children (<18 years old).

Use in elderly men:
Dosage adjustments are not required in elderly patients.

CONTRAINDICATION:
Use of sildenafil is contraindicated in patients with a known hypersensitivity to any component of the tablet. Sildenafil was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its administration to patients who are concurrently using nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently is therefore contraindicated (*see DRUG INTERACTIONS*).

WARNING & PRECAUTION:
A through 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.

Agent for the treatment of erectile dysfuntion should not be used in men for whom sexual activity is inadvisable. Serious cardiovascular events, including myocardial infarction, sudden cardiacdeath, ventricular arrhythmia,cerebrovascular hemorrhage and transient ischemic attack have been reported post-marketing in temporal association with the use of sildenafil for erectile dysfunction. Most, but not all, 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 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. Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilation 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. Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision or loss of vision, has been reported rarely post-marketing with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors such as low cup to disc ration ("crowded disk"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. No causal relationship has been made between use of PDE5 inhibitors and NAION. Physicians should discuss with patients the increased risk NAION in individuals who have already experienced NAION. The patients should be advised that in case of sudden visual loss, to stop taking sildenafil and consult a physician immediately. 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 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 (see DOSAGE AND ADMINISTRATION). In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms. 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 to patients with retinitis pigmentosa, therefore sildenafil should be administered with caution to these patients.

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 to patients with bleeding disorders or activepepticulceration, therefore sildenafil should be administered with caution to these patients.

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 with other treatments for erectile dysfuntion have not been The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied, and the use of such combinations is not recommended.

Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

Use in Pregnancy and Lactation:
Sildenafil is not indicated for use in women.
No teratogenic effects, impairment of fertility or adverse effects on peri/postnatal development were found in reproduction studies in rats and rabbits following oral administration of sildenafil. There are no adequate and well-controlled studies in pregnant or lactating women.

Effects on ability to drive and use machines:
The effect of sildenafil on the ability to drive and use machinery has not been studied.

SIDE EFFECTS:
The most common side effects are headache, flushing and dyspepsia. Other side effects include visual disturbances, dizziness, nasal congestion, diarrhoea, vomiting, swelling of the eyelids, pain and redness of the eyes, epistaxis, muscle pain, back pain, skin rashes, urinary-tract infection, syncope, cerebrovascular haemorrhage, and transient ischaemic attack. It may also cause priapism, palpitations and serious cardiovascular events including sudden cardiac death.The following adverse reactions were reported during post-marketing surveillance:

Immune system disorders: hypersensitivity reaction (including skin rash)
Nervous system disorders: seizure, seizure recurrence
Cardiac disorders: tachycardia
Vascular disorders: hypotension, syncope, epistaxis
Gastrointestinal disorders: vomiting
Eye disorders: eye pain, red eyes/bloodshot eyes
Reproductive system and breast disorders: prolonged erection and/or priapism.

DRUG INTERACTIONS:
Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates. Use of the two drugs between sildenafil and nicorandil should be avoided as the former may enhance the hypotensive effect of nicorandil. Symptomatic hypotension may also occur when sildenafil are given with alpha blockers. Drugs including cimetidine, delavirdine, erythromycin, itraconazole, ketoconazole, and HIV-protease inhibitors that inhibit the cytochrome P450 isoenzyme CYP3A4, may reduce the clearance of phosphodiesterase type-5 inhibitors. Hence, it required a reduction in dosage. Besides, the plasma concentrations of sildenafil are significantly increased by ritonavir and grapefruit juice whereas the plasma concentrations of sildenafil are likely decreased by inducers of CYP3A4 such as rifampicin. Thus, such combinations should not be given, unless necessary.

OVERDOSAGE AND TREATMENT:
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 it is not eliminated in the urine.

STORAGE:
Store below 30°C. Keep tablets in the original package, protected from moisture.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:
Available in blister pack of 1x4's and 1x6's.

Further information can be obtained from pharmacist, physician or the manufacturer.

Manufactured by & Product Holder :
Kotra Pharma (M) Sdn. Bhd. (90082-V)
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