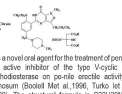
(For the use only of a registered Medical Practitioner or a Hospital or a Laboratory)
Sildenafil Citrate Tablets
DISFRUTAR 50^{TM}

COMPOSITION:
Each Film Coated Tablet Contains:-
Sildenafil Citrate BP
Eq. to Sildenafil..... 50 mg
Excipients..... q.s.

1. Description:
Sildenafil citrate is designated chemically as 1-[[3-(6, 7-dihydro-7-oxo-3-propyl-1H-pyrazolo [4, 3-d] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-Methylpiperazine and it is a popularly known as Viagra (Figure 1).



This is a novel oral agent for the treatment of penile erectile dysfunction (Boolell M et al., 1996). It is an active inhibitor of the type V-cyclic guanosine mono-phosphate (cGMP)-specific phosphodiesterase on pe-nile erectile activity and causes cGMP to accumulate corpus cavernosum (Boolell Met al.,1996, Turko Iet al.,1999, Lowentritt Bet al.,1999, Brock Get al.,2000). The structural formula is C22H30N6O4S. It is an ampholyte with pKa value 4 (pyridinium ion) and 8.8 (benzimidazole). Sildenafil citrate is twice more soluble in methanol than in water. Its solubility decreases with pH up to 9 when it starts to increase again. A few me-thods based on HPLC were reported for the determina-tion of sildenafil citrate in biological and pharmaceuti-cal products. A reverse-phase HPLC method using ace-tonitrile-phosphate buffer-water (28:4.68 v/v/v) with detection at 230 nm was utilized for the simultaneous determination for sildenafil and its metabolite (UK-103,320) using the automated sequential trace enrichment of dialysates(Cooper J etal.,1997). Re-verse-phase HPLC method using 70 mM potassium phosphate monobasic buffer of pH 3.0 containing 100 mM triethylamine: acetonitrile (7.3 v/v) as the mobile phase at 225 nm for the separation of sildenafil citrate formed due to oxidation (Martel A et al.,1997). RP-HPLC method for the determination of sildenafil citrate by using Lichrospher C18 column with water-acetonitrile as the mobile phase and UV detection at 245 nm (Dinesh N et al., 2002). A reverse-phase HPLC method for the determination of its related substances in commercial for mulations and tablets was reported (Draghmoh Net al.,2001). The method was developed utilizing a monolithic silica column and an isocratic elu-tion of acetonitrile: water and detection at 292 nm with a flow rate of 2.0 ml/m.

2. Indication and usage:
Treatment of men with 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.

3. Contraindication:
Hypersensitivity to the active substance or to any of the excipients.
Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form is therefore contraindicated.
Agents for the treatment of erectile dysfunction, including sildenafil, should not be used in men for whom sexual activity is inadvisable (e.g. patients with severe cardiovascular disorders such as unstable angina or severe cardiac failure).
Sildenafil is contraindicated in patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).
The safety of sildenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated: severe hepatic impairment, hypotension (blood pressure < 90/50 mmHg), recent history of stroke or myocardial infarction and known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

4. Posology and method of administration
Posology
This strength is not suitable for dosages below 50 mg.
Other medicinal products of Sildenafil in adequate strength are available.
Use in adults
The recommended dose is 50mg taken as needed approximately one hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100mg or decreased to 25mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day. If Sildenafil is taken with food, the onset of activity may be delayed compared to the fasted state.
Special populations
Elderly patientsDosage adjustments are not required in elderly patients (≥ 65 years old).
Patients with renal impairment The dosing recommendations described in "Use in adults" apply to patients with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min).
Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 ml/min) a 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased to 50mg and 100mg as necessary.
Patients with hepatic impairmentSince sildenafil clearance is reduced in patients with hepatic impairment (e.g. cirrhosis) a 25mg dose should be considered. Based on efficacy andtolerability, the dose may be increased step-wise to 50mg and 100mg as necessary.
Paediatric population
Sildenafil is not indicated for individuals below 18 years of age.
Use in patients using other medicines
With the exception of ritonavir for which co-administration with sildenafil is not advised a starting dose of 25mg should be considered in patients receiving concomitant treatment with CYP3A4 inhibitors.
In order to minimise the potential for developing postural hypotension in patients receiving alpha-blocker treatment, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25 mg should be considered.
Method of administration
For oral use.

5. Warning and Precautions:
A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.
Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure.Prior to prescribing sildenafil, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory 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.
Sildenafil potentiates the hypotensive effect of nitrates.
Serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported post-marketing in temporal association with the use of Sildenafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many events were reported to occur during or shortly after sexual intercourse and a few were reported to occur shortly after the use of Sildenafil without sexual activity. It is not possible to determine whether these events are related directly to these factors or to other factors.
Agents for the treatment of erectile dysfunction, including 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 anaemia, multiple myeloma or leukaemia).
The safety and efficacy of combinations of sildenafil with other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.
Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy have been reported in connection with the intake of sildenafil and other PDE5 inhibitors. The patient should be advised that in case of sudden visual defect, he should stop taking Sildenafil and consult a physician immediately.
Co-administration of sildenafil with ritonavir is not advised.
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. This is most likely to occur within 4 hours post sildenafil dosing. In order to minimise the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Initiation of sildenafil at a dose of 25 mg should be considered. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.
Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside in vitro. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Therefore sildenafil should be administered to these patients only after careful benefit-risk assessment.
The film coating of the Sildenafil tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Sildenafil is not indicated for use by women.
6. Adverse drug reactions:
Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor used for the treatment of erectile dysfunction.
Side effects of Sildenafil include:
- warmth or redness in the face, neck, or chest,
- stuffy nose,
- headaches,
- stomach pain,
- upset stomach,
- nausea
- diarrhea
- memory problems,
- back pain,
- an inability to differentiate between the colors green and blue,
- loss of hearing,
- ringing in the ears,
- dizziness.

7. Drug Interaction
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 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.
In vivo studies:
Population pharmacokinetic analysis of clinical trial data indicated a reduction in sildenafil clearance when co-administered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, cimetidine). Although no increased incidence of adverse events was observed in these patients, when sildenafil is administered concomitantly with CYP3A4 inhibitors, a starting dose of 25mg should be considered.
Co-administration of the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500mg twice daily) with sildenafil (100mg single dose) resulted in a 300% (4-fold) increase in sildenafil Cmax and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200ng/ml, compared to approximately 5ng/ml when sildenafil was administered alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is not advised and in any event the maximum dose of sildenafil should under no circumstances exceed 25mg within 48 hours.
Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200mg three times a day) with sildenafil (100mg 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.
When a single 100mg dose of sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500mg twice daily for 5 days), there was a 182% increase in sildenafil systemic exposure (AUC). In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC, Cmax, Tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50mg) to healthy volunteers.
Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil.
Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil.
Although specific interaction studies were not conducted for all medicinal products, population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin, phenytoin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).
Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have serious interaction with sildenafil.
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.
There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.
In vivo studies:
Consistent with its known effects on the nitric oxide/cGMP pathway , sildenafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors or nitrates in any form is therefore contraindicated.
Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. This is most likely to occur within 4 hours post sildenafil dosing. 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, 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 light-headedness, but not syncope.
No significant interactions were shown when sildenafil (50mg) was co-administered with tolbutamide (250mg) or warfarin (40mg), both of which are metabolised by CYP2C9.
Sildenafil (50mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150mg).
Sildenafil (50mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum blood alcohol levels of 80 mg/dl.
Pooling of the following classes of antihypertensive medication; diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists, antihypertensive medicinal products (vasodilator and centrally-acting), adrenergic neurone blockers, calcium channel blockers and alpha-adrenoceptor blockers, showed no difference in the side effect profile in patients taking sildenafil compared to placebo treatment. In a specific interaction study, where sildenafil (100mg) was co-administered with amlodipine in hypertensive patients, there was an additional reduction on supine systolic blood pressure of 8 mmHg. The corresponding additional reduction in supine diastolic blood pressure was 7 mmHg. These additional blood pressure reductions were of a similar magnitude to those seen when sildenafil was administered alone to healthy volunteers.
Sildenafil (100mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

8. Use in specific populations:
Sildenafil is not indicated for use by women.
No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

9. Overdosage:
Symptoms
Symptoms observed after an overdose of cetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect. Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.
Management
There is no known specific antidote to cetirizine. Should overdose occur symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence. Alternatively consider activated charcoal.
Cetirizine is not effectively removed by dialysis.

10. PHARMACOLOGICAL PROPERTIES:
Pharmacodynamics properties:
Penile erection is a hemodynamic process initiated by the relaxation of smooth muscle in the corpus cavernosum and its associated arterioles. During sexual stimulation, nitric oxide is released from nerve endings and endothelial cells in the corpus cavernosum. Nitric oxide activates the enzyme guanylate cyclase resulting in increased synthesis of cyclic guanosine monophosphate (cGMP) in the smooth muscle cells of the corpus cavernosum. The cGMP in turn triggers smooth muscle relaxation, allowing increased blood flow into the penis, resulting in erection. The tissue concentration of cGMP is regulated by both the rates of synthesis and degradation via phosphodiesterases (PDEs). The most abundant PDE in the human corpus cavernosum is the cGMP-specific PDE5; therefore, the inhibition of PDE5 enhances erectile function by increasing the amount of cGMP. Because sexual stimulation is required to initiate the local release of nitric oxide, the inhibition of PDE5 has no effect in the absence of sexual stimulation.
The pharmacodynamic effects of Sildenafil Citrate and its main circulating metabolites M1, M4 and M5 were determined during a series of in vitro and in vivo experiments in animals. Results of these studies conducted indicate that Sildenafil Citrate exerts PDE5 inhibiting activity. This causes smooth muscle relaxation, inducing a rise in intracavernosal pressure and consequently penile erection. Some of these studies used sildenafil and tadalafil as comparators. In these studies an IC50 (PDE5 inhibition)= 0.89 nM (human recombinant enzyme) was observed for Sildenafil Citrate compared to an IC50=8.5 nM and IC50=9.4 nM for sildenafil and tadalafil, respectively. The metabolites M1, M4, and M5 showed a potency of 3.6, 18, and 20 fold less than the parent compound in inhibiting human recombinant PDE5, respectively.
No study has been conducted to assess possible effects of Sildenafil Citrate on other potential therapeutic indications.
In vitro studies:
Studies in isolated human and rabbit corpus cavernosum slices demonstrated that Sildenafil Citrate dose dependently increased the concentration of cGMP, both in unstimulated and in stimulated slices. Rabbit tissue was found to be less sensitive to Sildenafil Citrate than human tissue.
Electrophysiological studies were also conducted in a human cell line (HEK293) transfected with human hERG gene to address the direct influence of Sildenafil Citrate on the repolarizing ikr current. Sildenafil was used as a comparator. Block of the hERG channel was shown at IC50=84 μM for Sildenafil Citrate and IC50=111 μM for sildenafil (not statistically significantly different). If the threshold concentrations are considered, the hERG-blockade becomes apparent at 3 μM, a concentration about 88-fold above the peak plasma level in man at the highest clinically recommended dose of 20 mg. Taking into account these results, the potential for QT prolongation in humans can be considered low. Regarding Sildenafil Citrate's main metabolites, the risk for QT prolongation has been studied in vivo in precinical studies at multiples of the maximum therapeutic dose. In terms of Cmax, M1 and M4 were assessed at 21 and 14 times the maximum therapeutic dose. ECG analysis did not reveal any potential for QT prolongation.
In vivo studies
A new animal model using conscious adult male rabbits was developed to evaluate the efficacy of Sildenafil Citrate in vivo. This new animal model has been validated and sildenafil was tested as a standard and found to be active inthe model. In this rabbit model the maximal erection achievable with sildenafil was half of that achieved with Sildenafil Citrate, and for sildenafil 3-5 times higher doses were needed to achieve comparable effects.
Pharmacokinetics properties:
Absorption
Sildenafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The mean absoluto oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100mg).
When sildenafil is taken with food, the rate of absorption is reduced with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29%.
Distribution
The mean steady state volume of distribution (Vd) for sildenafil is 105 l, indicating distribution into the tissues. After a single oral dose of 100 mg, the mean maximum total plasma concentration of sildenafil is approximately 440 ng/ml (CV 40%). Since sildenafil (and its major circulating N-desmethyl metabolite) is 96% bound to plasma proteins, this results in the mean maximum free plasma concentration for sildenafil of 18 ng/ml (38 nM). Protein binding is independent of total drug concentrations.
In healthy volunteers receiving sildenafil (100mg single dose), less than 0.0002% (average 188ng) of the administered dose was present in ejaculate 90 minutes after dosing.
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. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% that of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil. The N-desmethyl metabolite is further metabolised, with a terminal half life of approximately 4 h.
Elimination
The total body clearance of sildenafil is 41 l/h with a resultant terminal phase half life of 3-5 h. 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).
Pharmacokinetics in special patient groups
Elderly
Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.
Renal insufficiency
In volunteers with mild to moderate renal impairment (creatinine clearance = 30-80 ml/min), the pharmacokinetics of sildenafil were not altered after receiving a 50mg single oral dose. The mean AUC and Cmax of the N-desmethyl metabolite increased 126% and 73% respectively, compared to age-matched volunteers with no renal impairment. However, due to high inter-subject variability, these differences were not statistically significant. In volunteers with severe renal impairment (creatinine clearance < 30 ml/min), sildenafil clearance was reduced, resulting in mean increases in AUC and Cmax of 100% and 88% respectively compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 79% and 200% respectively.
Hepatic insufficiency
In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function have not been studied.

11. How to supplied:
Each Blister strip contains 5 Tablets.

12. SHELF LIFE: Refer to carton & strip.

13. Storage: Store below 25°C. Protect from light.

PRODUCTO HECHO EN LA INDIA PARA AREA Y
EMPRESA ESPECIALISTA BI MEDICA GUATEMALA

Número de registro.:
Código neutral: HPI/Drugs/09/92

Manufactured for: Area Biotech Pvt Ltd.
Marketed and Exported By:
AREA IMPORTERS & EXPORTERS PVT. LTD.
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