

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

Androz Tablet 50 mg
Androz Tablet 100 mg
(Sildenafil Tablets 50 mg/100 mg)

COMPOSITION

Androz Tablet 50 mg

Each film coated tablet contains:

Sildenafil citrate Ph.Eur. equivalent to Sildenafil 50 mg

Colours: Lake of Indigo Carmine and Titanium dioxide

Excipients q.s

Androz Tablet 100 mg

Each film coated tablet contains:

Sildenafil citrate Ph.Eur: equivalent to Sildenafil..... 100 mg

Colours: Lake of Indigo Carmine and Titanium dioxide

Excipients q.s.

PHARMACEUTICAL FORM

Film coated Tablets

PRODUCT DESCRIPTION

Androz Tablet 50 mg:

Blue, round biconvex, film coated tablets, debossed with '8' bisect '7' on one side and plain on other side.

Androz Tablet 100 mg:

Blue, round biconvex, film coated tablets, debossed with '8' bisect '8' on one side and plain on other side.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.

ATC Code: G04B E03.

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 level 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 carvenosum, resulting in smooth muscle relaxation and inflow of blood to the carvenosum, Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Sildenafil invitro 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 4,000-fold selectively for PDE5 versus PDE3 is important because PDE3 is involved in the control of cardiac contractility.

PHARMACOKINETICS

Sildenafil pharmacokinetics is 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, sildenafil.

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 3.5 nM. In man the mean maximum free plasma concentration of sildenafil following a single oral dose of 100 mg is approximately 18 ng/mL or 38 nM

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 T_{max} of 60 minutes and a mean reduction in C_{max} of 29%, however the extent of absorption was not significantly affected (AUC decreased by 11%).

Distribution

The mean steady state volume of distribution (V_{ss}) 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. 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 metabolized, with a terminal half-life of approximately 4 hours.

Elimination

The total body clearance of sildenafil is 41l/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 feces (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

Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal insufficiency

Mild (creatinine clearance = 50-80 mL/min) and moderate (creatinine clearance=30-49 mL/min) renal impairment, the pharmacokinetics of single oral dose of sildenafil (50 mg) were not altered. Severe renal impairment (creatinine clearance =<30 mL/min), sildenafil clearance was reduced resulting in approximately doubling of AUC (100%) and C_{max} 88%) compared with no renal impairment.

In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200 % and 79% respectively with severe renal impairment compared with normal renal functions.

Hepatic insufficiency

Mild to moderate hepatic cirrhosis (Child-Pugh A and B) sildenafil clearance was reduced, resulting in increases in AUC (85%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

INDICATION

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.

DOSE AND METHOD OF ADMINISTRATION

Sildenafil tablets are for oral administration.

Posology

Use in adults

For most patients, the recommended dose is 50 mg 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 100 mg or decreased to 25 mg. The maximum recommended daily dose is 100 mg. The maximum recommended dosing frequency is once per day.

Use in patients with impaired renal function

Dosage adjustment are not required in patients with mild to moderate renal impairment (creatinine = 30-80 ml/min).

Since sildenafil clearance is reduced in patients with severe renal impairment (creatinine clearance <30mL/min), a 25 mg 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 25 mg dose should be considered.

Use in patients using other medications

Given the extent of the interaction with patients receiving concomitant therapy with ritonavir it is recommended not to exceed a maximum single dose of 25 mg of sildenafil in a 48-hour period.

A starting dose of 25 mg should be considered in patients receiving concomitant treatment with CYP 3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole, Itraconazole).

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.

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.

Method of administration

For oral use.

CONTRAINDICATIONS

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.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

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.

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).

WARNINGS 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.

Cardiovascular risk factors

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.

Priapism

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).

Prolonged erections and priapism have been reported with sildenafil in post-marketing experience. In the event of an erection that persists for 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 could result.

Concomitant use with other PDE5 inhibitors or other treatments for erectile dysfunction

The safety and efficacy of combinations of sildenafil with other PDE5 inhibitors, or other pulmonary arterial hypertension (PAH) treatments containing sildenafil, or other treatments for erectile dysfunction have not been studied. Therefore the use of such combinations is not recommended.

Effects on vision

Cases of visual defects have been reported spontaneously in connection with the intake of sildenafil and other PDE5 inhibitors. Cases of non-arteritic anterior ischaemic optic neuropathy, a rare condition, have been reported spontaneously and in an observational study in connection with the intake of sildenafil and other PDE5 inhibitors. Patients should be advised that in the event of any sudden visual defect, they should stop taking sildenafil and consult a physician immediately.

Concomitant use with ritonavir

Co-administration of sildenafil with ritonavir is not advised.

Concomitant use with alpha-blockers

Caution is advised when sildenafil is administered to patients taking an alpha-blocker, as the co-administration 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.

Effect on bleeding

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.

Women

Sildenafil is not indicated for use by women.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Because of dizziness and altered vision were reported adverse effect with sildenafil, patients should be aware of how they react to Sildenafil, before driving or operating machinery.

DRUG INTERACTIONS

Effects of other medicinal products on sildenafil

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 and inducers of these isoenzymes may increase sildenafil clearance.

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 treatment 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 result in a 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 ($IC_{50} > 150 \mu M$). Given sildenafil peak plasma concentrations of approximately $1 \mu M$ 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.

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 use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated.

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

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

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

USE IN SPECIFIC POPULATIONS

Sildenafil is not indicated for use by women.

There are no adequate and well-controlled studies in pregnant or breastfeeding women.

No relevant adverse effects were found in reproduction studies in rats and rabbits following oral administration of sildenafil.

ADVERSE REACTIONS

System Class	Organ	Very common	Common	Uncommon	Rare
Infections and infestations				Rhinitis	
Immune system disorders				Hypersensitivity	
Nervous system disorders		Headache	Dizziness	Somnolence, Hypoaesthesia	Cerebrovascular accident, Transient ischaemic attack, Seizure*, Seizure recurrence*, Syncope
Eye disorders			Visual colour distortions**, Visual disturbance, Vision blurred	Lacrimation disorders***, Eye pain, Photophobia, Photopsia, Ocular hyperaemia, Visual brightness, Conjunctivitis	Non-arteritic anterior ischaemic optic neuropathy (NAION)*, Retinal vascular occlusion, Retinal haemorrhage, Arteriosclerotic retinopathy, Retinal disorder, Glaucoma, Visual field defect, Diplopia, Visual acuity reduced, Myopia, Asthenopia, Vitreous floaters, Iris disorder, Mydriasis, Halo

				vision, Eye oedema, Eye swelling, Eye disorder, Conjunctival hyperaemia, Eye irritation, Abnormal sensation in eye, Eyelid oedema, Scleral discoloration
Ear and labyrinth disorders			Vertigo, Tinnitus	Deafness
Cardiac disorders			Tachycardia, Palpitations	Sudden cardiac death, Myocardial infarction, Ventricular arrhythmia, Atrial fibrillation, Unstable angina
Vascular disorders		Flushing, Hot flush	Hypertension, Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis, Sinus congestion	Throat tightness, Nasal oedema, Nasal dryness
Gastrointestinal disorders		Nausea, Dyspepsia	Gastro oesophageal reflux disease, Vomiting, Abdominal pain upper, Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	Stevens-Johnson Syndrome (SJS)*, * Toxic Epidermal Necrolysis (TEN)
Musculoskeletal and connective tissue disorders			Myalgia, Pain in extremity	
Renal and urinary disorders			Haematuria	
Reproductive system and breast				Penile haemorrhage,

disorders				Priapism, Haemospermia, Erection increased
General disorders and administration site conditions			Chest pain, Fatigue, Feeling hot	Irritability
Investigations			Heart rate increased	

**Visual colour distortions: Chloropsia, Chromatopsia, Cyanopsia, Erythropsia and Xanthopsia

***Lacrimation disorders: Dry eye, Lacrimal disorder and Lacrimation increased

OVERDOSE

In single dose, doses up to 800 mg, adverse reactions were similar to those seen at lower doses, but the incidence rates and severities were increased. Doses of 200 mg did not result in increased efficacy but the incidence of adverse reactions (headache, flushing, dizziness, dyspepsia, nasal congestion, altered vision) was increased.

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 not eliminated in the urine.

EXPIRY DATE

2 Years from the date of manufacturing.

STORAGE

Keep out of the reach and sight of children.
Store below 30 °C.

PRESENTATION

Androz 50 mg and 100 mg tablets are available in blister strip of 1x4, 2x4 and 3x4 tablets Not all presentations may be available locally.

DATE OF REVISION

11/05/2016

MANUFACTURED BY



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