

1. NAME OF THE MEDICINAL PRODUCT

ANIVEGA 100 TABLETS (Sildenafil Tablets BP 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Film Coated Tablet Contains:

Sildenafil Citrate BP equivalent to Sildenafil 100 mg

Approved colour used.

Excipients.....Q.S.

Excipients with known effect: Lactose Monohydrate

3. PHARMACEUTICAL FORM: Film coated tablets

Description: Blue coloured, diamond shaped, biconvex, film coated tablet embossing "100" on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications:

ANIVEGA 100 TABLETS (Sildenafil Tablets BP 100 mg) are indicated for the treatment of Erectile dysfunction in men.

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

4.2 Posology and method of administration

Posology

Use in adults

The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. Based on efficacy and toleration, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once per day.

Use in patients with impaired renal function

Dosage adjustments are not required in 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 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 the CYP3A4 inhibitors (e.g. erythromycin, saquinavir, ketoconazole, itraconazole)

Method of administration

For oral use.

4.3 Contraindications

ANIVEGA 100 TABLETS (Sildenafil Tablets BP 100 mg) are contraindicated in:

Hypersensitivity to the active substance or to any of the excipients used in the formulation.

Co-administration with nitric oxide donors (such as amyl nitrite) or nitrates in any form due to the hypotensive effects of nitrates.

Combination with the most potent of the CYP3A4 inhibitors (eg, ketoconazole, Itraconazole, ritonavir).

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,

Recent history of stroke or myocardial infarction,

Severe hypotension (blood pressure < 90/50 mmHg) at initiation.

4.4 Special warnings and precautions for use

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 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 (REVATIO), 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.

The film coating of the tablet contains lactose. Sildenafil should not be administered to men with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Women

Sildenafil is not indicated for use by women.

4.5 Interaction with other medicinal products and other forms of interaction

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 and inducers of these isoenzymes may increase 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). However, there was no increased incidence of adverse events in these patients. Cimetidine (800 mg), a cytochrome P450 inhibitor and a non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) to healthy volunteers. Coadministration with the HIV protease inhibitor ritonavir, which is a highly potent P450 inhibitor, at steady state (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a 300% (4-fold) increase in sildenafil C_{max} and a 1000% (11-fold) increase in sildenafil plasma AUC. At 24 hours, the plasma levels of sildenafil were still approximately 200 ng/mL, compared to approximately 5 mg/mL when sildenafil was dosed alone. This is consistent with ritonavir's marked effects on a broad range of P450 substrates. Sildenafil had no effect on ritonavir pharmacokinetics. Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200mg three times daily) with sildenafil (100mg single dose) resulted in a 140% increase in sildenafil C_{max} 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 the dose of sildenafil for subjects receiving potent CYP3A4 inhibitors was administered as recommended, the maximum free plasma sildenafil concentration did not exceed 200 nM for any individual and was consistently well tolerated. Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil. Population pharmacokinetic analysis showed no effect of concomitant medication on sildenafil pharmacokinetics when grouped as CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, betaadrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates).

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its major circulating metabolite.

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.

In vivo studies:

Sildenafil was shown to potentiate the hypotensive effects of acute and chronic nitrates, therefore use of nitric oxide donors, organic nitrates or organic nitrites in any form either regularly or intermittently with Sildenafil is contraindicated. In three specific drug-drugs 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 lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. No significant interactions were shown when sildenafil (50mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolised by CYP2C9. Sildenafil (100 mg) did not effect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Sildenafil (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg). Sildenafil (50 mg) did not potentiate the hypotensive effects of alcohol in healthy volunteers with mean maximum

blood alcohol levels of 80 mg/dL. No interaction was seen when sildenafil (100 mg) was co-administered with amlodipine in hypertensive patients. The mean additional reduction on supine blood pressure (systolic, 8 mmHg; diastolic, 7 mmHg) was of a similar magnitude to that seen when sildenafil was administered alone to healthy volunteers.

Analysis of the safety data base showed no difference in the side effect profile in patients taking sildenafil with and without anti-hypertensive medication.

4.6 Pregnancy and Lactation

Pregnancy

Sildenafil is not indicated for use by women.

Lactation

Sildenafil is not indicated for use by women.

Fertility

Sildenafil is not indicated for use by women.

There was no effect on sperm motility or morphology after single 100 mg oral doses of sildenafil in healthy volunteers.

4.7 Effects on the ability to drive and use machines

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

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to Sildenafil, before driving or operating machinery.

4.8 Undesirable effects

The most common side effects are headache, flushing, heartburn, stomach upset, nasal stuffiness, lightheadedness, dizziness and diarrhea.

4.9 Overdoses

In studies with healthy volunteers, of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group : Urologicals; Drugs used in erectile dysfunction. ATC Code: G04BE03

Sildenafil is an oral therapy for erectile dysfunction. In the natural setting, i.e. with sexual stimulation, it restores impaired erectile function by increasing blood flow to the penis.

The physiological mechanism responsible for erection of the penis involves the 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 is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) in the corpus cavernosum, where PDE5 is responsible for degradation of cGMP. Sildenafil has a peripheral site of action on erections. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but potently enhances the relaxant effect of NO on this tissue. When the NO/cGMP pathway is activated, as occurs with sexual stimulation, inhibition of PDE5 by sildenafil results in increased corpus cavernosum levels of cGMP. Therefore sexual stimulation is required in order for sildenafil to produce its intended beneficial pharmacological effects.

5.2 Pharmacokinetic properties

Absorption and Bioavailability

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 absolute oral bioavailability is 41% (range 25-63%). After oral dosing of sildenafil AUC and C_{max} 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 T_{max} of 60 minutes and a mean reduction in C_{max} of 29%.

Distribution

The mean steady state volume of distribution (V_d) 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).

Special Population

Geriatrics: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

Renal Insufficiency: In volunteers with mild (CL_{cr}=50-80 mL/min) and moderate (CL_{cr}=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of **Sildenafil Tablets BP 100 mg** were not altered. In volunteers with severe (CL_{cr}<30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients.

5.3 Preclinical safety Data:

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch, Microcrystalline cellulose, Calcium hydrogen phosphate dihydrate, Povidone (K 30), Methyl hydroxybenzoate, Propyl hydroxybenzoate, Purified talc, Magnesium stearate, Croscarmellose sodium, Sodium starch glycolate, Colloidal anhydrous silica, Hypromellose (15 CPS), Titanium dioxide, Indigo carmine & Macrogol 6000.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in a dry & dark place.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

Packing:

Primary packing: 4 Tablets in an ALU-PVC blister.

Secondary packing: 1 Blister is packed in an inner carton along with leaflet.

Tertiary packing: 10 Inner cartons are packed in an outer carton. Shrink individual outer carton. Such 100 shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strapp with strapping roll.

6.5 Special precautions for disposal and other handling

No special requirements.

7. Applicant / Manufacturer

Applicant

Name and address	M/s. ANISUN PHARMACEUTICALS CO. NIG. LTD. No.29, Heritage Avenue Omagba Phase II, Onitsha, Anambra State
Tel	+234 8033476994
Fax	--
Email	anisunpharm2013@gmail.com

Manufacturer

Name and address	M/s. IMPULSE PHARMA PVT. LTD. J-201, J-202/1, MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India
Tel	+91-7350864803
Fax	--
Email	pravin.patil@kamlagroup.co.in