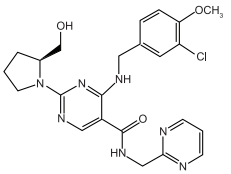
Avafil™
(A v a n a f i l)

ایوافِل

Tablets 50mg, 100mg, & 200mg

DESCRIPTION
Avafil (Avanafil) is a selective inhibitor of cGMP-specific PDE5. Avanafil is chemically described as (S)-4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide. Its molecular formula is $C_{23}H_{26}ClN_7O_3$ and the structural formula is:



Avanafil

QUALITATIVE AND QUANTITATIVE COMPOSITION
Avafil (Avanafil) Tablets are available for oral administration as:

Avafil Tablets 50mg
Each tablet contains:
Avanafil…50mg

Avafil Tablets 100mg
Each tablet contains:
Avanafil…100mg

Avafil Tablets 200mg
Each tablet contains:
Avanafil…200mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by Avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation.

Pharmacokinetics
Absorption
Avanafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 0.5 to 0.75 hours of oral dosing in the fasted state. When Avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200mg). There was no effect on the extent of exposure (AUC). The small changes in Avanafil C_{max} are considered to be of minimal clinical significance.

Distribution
Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total active substance concentrations, age, renal and hepatic function. Avanafil was not found to accumulate in plasma when dosed 200mg twice daily over 7 days. Based upon measurements of Avanafil in semen of healthy volunteers 45-90 minutes after dosing, less than 0.0002% of the administered dose may appear in the semen of patients.

Metabolism
Avanafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite shows a phosphodiesterase selectivity profile similar to that of Avanafil and an in vitro inhibitory potency for PDE5 18% of that of Avanafil. Therefore, M4 accounts for approximately 4% of total pharmacologic activity. The M16 metabolite was inactive against PDE5.

Elimination
Avanafil is extensively metabolised in humans. After oral administration, Avanafil is excreted as metabolites predominantly in the feces (approximately 63% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose).

Special Population
Elderly
Older patients (65 years or over) had comparable exposure to that seen in younger patients (18-45 years). However, data on subjects older than 70 years are limited.

Patients with Renal impairment
In subjects with mild (creatinine clearance ≥ 50 - < 80mL/min) and moderate (creatinine clearance ≥ 30 - < 50mL/min) renal impairment, the pharmacokinetics of a single 200mg dose of Avanafil were not altered. There are no data available for subjects with severe renal insufficiency or end-stage renal disease on haemodialysis.

Patients with Hepatic impairment
Subjects with mild hepatic impairment (Child-Pugh A) had comparable exposure to subjects with normal hepatic function when a single dose of 200mg Avanafil was administered. The exposure 4 hours post-dose was lower in subjects with moderate hepatic impairment (Child-Pugh B) compared to subject with normal hepatic function after 200mg of Avanafil. The maximum concentration and exposure was similar to that observed after subjects with normal hepatic function received an efficacious Avanafil 100mg dose.

THERAPEUTIC INDICATIONS
Avafil (Avanafil) is indicated for the treatment of erectile dysfunction in adult males.
In order for Avafil (Avanafil) to be effective, sexual stimulation is required.

DOSAGE & ADMINISTRATION
The recommended starting dose is 100mg. Avafil (Avanafil) should be taken orally as needed as early as approximately 15 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to 200mg taken as early as approximately 15 minutes before sexual activity, or decreased to 50mg taken approximately 30 minutes before sexual activity. The lowest dose that provides benefit should be used. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.
Avafil (Avanafil) may be taken with or without food. If taken with food, the onset of activity may be delayed compared to to the fasted state.

Special Population
Elderly (≥ 65 years old)
Dose adjustments are not required in elder patients. Limited data are available in elder patients aged 70 years or above.

Renal impairment
Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30mL/min). Avanafil is contraindicated in patients with severe renal impairment (creatinine clearance < 30mL/min). Patients with mild or moderate renal impairment (creatinine clearance ≥30mL/min but <80mL/min) who were enrolled in phase 3 studies showed decreased efficacy compared to those with normal renal function.

Hepatic impairment
Avanafil is contraindicated in patients with severe hepatic impairment (Child Pugh class C). Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum efficacious dose and adjust posology based on tolerance.

Use in men with diabetes
Dose adjustments are not required in diabetic patients.

Pediatric
Avanafil is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years has not been established.

Concomitant use of CYP3A4 inhibitors
For patients taking concomitant strong CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin), do not use Avanafil. For patients taking concomitant moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of Avanafil is 50mg, not to exceed once every 24 hours.

ADVERSE REACTIONS
Common
Headache, flushing and nasal congestion.

Uncommon
Dizziness, somnolence, sinus headache, vision blurred, palpitations, hot flush, sinus congestion, dyspnoea exertional, dyspepsia, nausea, vomiting, stomach discomfort, back pain, muscle tightness, fatigue, hepatic enzyme increased, electrocardiogram abnormal and heart rate increased.

Rare
Influenza, nasopharyngitis, seasonal allergy, gout, insomnia, premature ejaculation, inappropriate affect, psychomotor hyperactivity, angina pectoris, tachycardia, hypertension, rhinorrhoea, upper respiratory tract congestion, epistaxis, dry mouth, gastritis, abdominal pain lower, diarrhoea, rash, flank pain, myalgia, muscle spasms, pollakiuria, penis disorder, spontaneous penile erection, pruritus genital, asthenia, chest pain, influenza like illness, oedema peripheral, blood pressure increased, blood in urine present, cardiac murmur, prostate specific antigen increased, weight increased, blood bilirubin increased, blood creatinine increased and body temperature increased.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Avanafil is contraindicated in below:
- Patients with hypersensitivity to the active substance or to any the excipient of the product.
- Patients who are using any form of organic nitrate or nitric oxide donors (such as amyl nitrite).
- The co-administration of type 5 phosphodiesterase (PDE5) inhibitors, including Avanafil, with guanylate cyclase stimulators, such as riociguat is contraindicated as it may potentially lead to symptomatic hypotension.
- Patients with severe hepatic impairment (Child-Pugh C).
- Patients with severe renal impairment (creatinine clearance < 30 mL/min).
- Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.
- Patients with known hereditary degenerative retinal disorders.
- Patients who are using potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin).
- Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease before prescribing Avanafil.

The use of Avanafil is contraindicated in:
- Patients who have suffered from a myocardial infarction, stroke, or lifethreatening arrhythmia within the last 6 months;
- Patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

PRECAUTIONS

Cardiovascular Risk

There is a potential for cardiac risk during sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for ED, including Avanafil, should not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

As with other PDE5 inhibitors Avanafil has systemic vasodilatory properties and may augment the blood pressure-lowering effect of other anti-hypertensive medications. Physicians should carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Alpha-Blockers and Other Antihypertensives

Physicians should discuss with patients the potential for Avanafil to augment the blood pressure-lowering effect of alpha-blockers and other antihypertensive medications. Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. Phosphodiesterase type 5 inhibitors, including Avanafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting). Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Decreased or sudden loss of hearing

Patients should be advised to stop taking PDE5 inhibitors, including Avanafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors.

Visual problems

Visual defects, including Central Serous Chorioretinopathy (CSCR) and cases of nonarteritic anterior ischaemic optic neuropathy (NAION) have been reported in connection with the intake of PDE5 inhibitors. The patient should be advised that in case of sudden visual effects he should stop taking Avanafil and consult a physician immediately.

Priapism

Prolonged erection lasting 4 hours or more (priapism) has been reported with other PDE5 inhibitors. 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. Avanafil 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).

Effect on bleeding

In vitro studies with human platelets indicate that PDE5 inhibitors do not have an effect on platelet aggregation on their own, but at supratherapeutic doses they potentiate the anti-aggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, PDE5 inhibitors do not appear to affect bleeding time alone or in combination with acetylsalicylic acid. There is no safety information on the administration of Avanafil to patients with bleeding disorders or active peptic ulceration. Therefore, Avanafil should be administered to such patients only after careful benefit-risk assessment.

Concomitant use of CYP3A4 inhibitors

Avanafil metabolism is principally mediated by the CYP450 isoform 3A4 (CYP3A4). Inhibitors of CYP3A4 may reduce Avanafil clearance and increase plasma concentrations of Avanafil. For patients taking concomitant strong CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin), do not use Avanafil. For patients taking concomitant moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of Avanafil is 50mg, not to exceed once every 24 hours.

Concomitant use of alcohol

Consumption of alcohol in combination with Avanafil can increase the potential for symptomatic hypotension. Patients should be advised that concurrent use of Avanafil and alcohol may increase the likelihood of hypotension, dizziness, or syncope. Physicians should also advise patients on what to do in the event of postural hypotensive symptoms.

Concomitant use of other treatments for erectile dysfunction

The safety and efficacy of combinations of Avanafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Patients should be informed not to take Avanafil in such combinations.

Counseling Patients about Sexually Transmitted Diseases

The use of Avanafil offers no protection against sexually transmitted diseases. Counseling patients about the protective measures necessary to guard against sexually transmitted diseases, including Human Immunodeficiency Virus (HIV), should be considered.

Effects on ability to drive and use machines

Avanafil has minor influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with Avanafil, patients should be aware of how they react to Avanafil before driving or using machines.

Pregnancy

Avanafil is not indicated for use in females.

Nursing Mother

Avanafil is not indicated for use in females.

DRUG INTERACTIONS

Nitrates:

Administration of Avanafil to patients who are using any form of organic nitrate, is contraindicated. Avanafil was shown to potentiate the hypotensive effect of nitrates. In a patient who has taken Avanafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of Avanafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate hemodynamic monitoring.

Medicinal products reducing systemic blood pressure

As a vasodilator, Avanafil may reduce systemic blood pressure. If Avanafil is used in combination with another medicinal product which reduces systemic blood pressure, the additive effects may result in symptomatic hypotension (e.g. dizziness, lightheadedness, syncope or near-syncope).

Patients with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators including Avanafil.

Alcohol

Both alcohol and PDE5 inhibitors, including Avanafil, act as vasodilators. When vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., greater than 3 units) in combination with Avanafil can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including Avanafil, and alpha-adrenergic blocking agents are both vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g., dizziness, lightheadedness, fainting).

Antihypertensives other than alpha-blockers

Avanafil had no effect on the pharmacokinetics of amlodipine, but amlodipine increased the maximum and total exposure of Avanafil by 28% and 60%, respectively. Caution should be exercised when prescribing Avanafil in combination with antihypertensive agents.

Moderate CYP 3A4 Inhibitors

Erythromycin (500mg twice daily) increased Avanafil 200mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of Avanafil to approximately 8 hours in healthy volunteers. Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice are likely to increase Avanafil exposure.

Cytochrome P450 Inducers

The potential effect of CYP inducers on the pharmacokinetics of Avanafil was not evaluated. The concomitant use of Avanafil and CYP inducers is not recommended.

OVERDOSAGE

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance because Avanafil is highly bound to plasma proteins and is not significantly eliminated in the urine.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Avafil (Avanafil) Tablets 50mg are available in blister pack of 4's.
Avafil (Avanafil) Tablets 100mg are available in blister pack of 4's.
Avafil (Avanafil) Tablets 200mg are available in blister pack of 4's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

PAK-200023126

29-30/27,
K.I.A., Karachi,
Pakistan