Proposed Package Insert

Brand or Product Name
Ajenafil Chewable Tablet 25 mg
Ajenafil Chewable Tablet 50 mg
Ajenafil Chewable Tablet 100 mg

Name and Strength

Each chewable tablet 25 mg sildenafil formed in situ from 35.15 mg sildenafil citrate
Each chewable tablet 50 mg sildenafil formed in situ from 70.24 mg sildenafil citrate
Each chewable tablet 100 mg sildenafil formed in situ from 140.48 mg sildenafil citrate

Product Description

25 mg: White, triangular, with a side of 7.3 mm, biconvex, embossed with "25" on one side.
50 mg: White, triangular, with a side of 8.8 mm, biconvex, embossed with "50" on one side.
100 mg: White, triangular, with a side of 11.8 mm, biconvex, embossed with "100" on one side.

Pharmacodynamics/ Pharmacokinetics

Pharmacotherapeutic group: Selective Phosphodiesterase-5 (PDE-5) Inhibitor
ATC-code: G04B E03

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.

Pharmacokinetics

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 absolute 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 I, 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 tablets (100 mg single dose), less than 0.0002% (average 188 ng) of the administered dose was present in ejaculate 90 minutes after dosing.

Biotransformation

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 4h.

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).

Linearity/non-linearity

After oral dosing of sildenafil AUC and Cmax increase in proportion with dose over the recommended dose range (25-100 mg).

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=30-80mL/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 up to 126% and up to 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 by 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%) 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.

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.

Indication
Ajenafil Chewable Tablet is indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance.

In order for Ajenafil Chewable Tablet to be effective, sexual stimulation is required.

Recommended Dosage
Use in adults:
The recommended dose is 50 mg taken as needed approximately one hour before sexual activity. The tablets should be chewed before swallowed.
Based on efficacy and tolerability, 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. If Ajenafil Chewable tablet is taken with food, the onset of activity may be delayed compared to the fasted state.

Special populations
Use in the elderly:

Dosage adjustments are not required in elderly patients (≥ 65 years old).

Renal impairment

The dosing recommendations described in "Use in adults" apply to 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 <30 mL/min) a 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased to 50mg up to 100mg.

Hepatic impairment
Since sildenafil clearance is reduced in patients with hepatic impairment (e.g cirrhosis) a 25mg dose should be considered. Based on efficacy and tolerability, the dose may be increased to 50mg and 100mg.

Pediatric population
Ajenafil Chewable Tablet is not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products
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 minimize the potential of developing postural hypotension, patients should be stable on alpha-blocker therapy prior to initiating sildenafil treatment. In addition, initiation of sildenafil at a dose of 25mg should be considered.

Route of Administration
Oral administration

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.

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).

Ajenafil Chewable Tablet 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.

<u>Cardiovascular risk factors</u>
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.

Ajenafil Chewable Tablet 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 Ajenafil Chewable Tablet.

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 Ajenafil Chewable Tablet 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).

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

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. The patient should be advised that in the event of any sudden visual defect, they should stop taking Ajenafil Chewable Tablet 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.

Contains aspartame, a source of phenylalanine. May be harmful for people with phenylketonuria.

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Women

Ajenafil Chewable Tablet is not indicated for use by women.

Interactions with Other Medicaments

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 and inducers of these isoenzymes may increase sildenafil clerance.

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 25 mg should be considered.

Co-administration of 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 Cmax and a 1,000% (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 ng/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 25 mg within 48 hours.

Co-administration of the HIV protease inhibitor saquinavir, a CYP3A4 inhibitor, at steady state (1200 mg three times a day) with sildenafil (100 mg 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 100 mg dose of sildenafil was administered with erythromycin, a moderate CYP3A4 inhibitor, at steady state (500 mg 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 (500 mg daily for 3 days) on the AUC, Cmax, tmax, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite. Cimetidine (800 mg), a cytochrome P450 inhibitor and non-specific CYP3A4 inhibitor, caused a 56% increase in plasma sildenafil concentrations when co-administered with sildenafil (50 mg) 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 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). Therefore, concomitant administration of strong CYP3A4 inducers, such as rifampicin, is expected to cause greater decreases in plasma concentrations of sildenafil.

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 μM). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that Ajenafil Chewable Tablet 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 (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 (50 mg) 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 (100 mg) 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 (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Statement on usage during pregnancy and lactation
Ajenafil Chewable Tablet 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.
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Effects on 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 Ajenafil Chewable Tablet, before driving or operating machinery.

Adverse Effects/ Undesirable Effects
The most commonly reported adverse reactions in clinical studies among sildenafil treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, visual disorder and visual color distortion.

Adverse reactions of sildenafil tablets from post-marketing surveillance has been gathered covering an estimated period >9 years. Because not all adverse reactions are reported to the Marketing Authorisation Holder and included in the safety database, the frequencies of these reactions cannot be reliably determined.

n the table below all medically important adverse reactions, which occurred in clinical trials at an incidence greater than placebo are listed by system organ class and frequency (very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

In addition, the frequency of medically important adverse reactions reported from post-marketing experience is included as not known.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Medically important adverse reactions reported at an incidence greater than placebo in controlled clinical studies with sildenafil tablets and medically important adverse reactions reported through post marketing surveillance

System Organ Class	Adverse Reactions
Immune system disorders	
Rare	Hypersensitivity reactions
Nervous system disorders	
Very common	Headache
Common	Dizziness
Uncommon	Somnolence, hypoaesthesia
Rare	Cerebrovascular accident, syncope
Not known	Transient ischaemic attack, seizure, seizure recurrence
Eye disorders	
Common	Visual disorders, visual colour distortion
Uncommon	Conjunctival disorders, eye disorders, lacrimation disorders, other eye disorders
Not known	Non-arteritic anterior ischaemic optic neuropathy (NAION), retinal vascular occlusion, visual field defect
Ear and labyrinth disorders	
Uncommon	Vertigo, tinnitus
Rare	Deafness*
Vascular disorders	
Common	Flushing
Rare	Hypertension, hypotension
Cardiac disorders	
Uncommon	Palpitations, tachycardia
Rare	Myocardial infarction, atrial fibrillation
Not known	Ventricular arrhythmia, unstable angina, sudden cardiac death
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion
Rare	Epistaxis
Gastrointestinal disorders	
Common	Dyspepsia
Uncommon	Vomiting, nausea, dry mouth
Skin, subcutaneous and soft tissue disorders	
Uncommon	Skin rash
Not known	Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Reproductive system and breast disorders	
Not known	Priapism, prolonged erection
Uncommon	Haematospermia, penilehaemorrhage
General disorders and administration site conditions	
Uncommon	Chest pain, fatigue

Investigations

Uncommon	Heart rate increased

* Ear disorders: Sudden deafness. Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

Overdose and Treatment

In single dose volunteer studies of doses up to 800 mg with sildenafil tablets, 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.

Other Ingredients

Polacrilin potassium, Magnesium stearate, Colloidal Anhydrous Silica, Aspartame, Croscarmellose Sodium, Peppermint Flavour, Lactose monohydrate, Povidone K-30.

Storage Conditions

Store below 30^{O}C in the original package to protect from light.

Dosage forms and packaging available

Chewable tablet, 4s/pack

Manufactured by:

Genepharm S.A.
18 km Marathon Avenue, 15351 Pallini Attikis, Greece

Product Registration Holder/ Imported by:

AJ Research & Pharma Sdn. Bhd.
Unit 27.1, Level 27, Menara Felda,
Platinum Park, No. 11, Persiaran KLCC,
50088 Kuala Lumpur
Malaysia

Date of revision of PI

December 2022