ZYDENA®

(Udenafil) Tablets
100 mg / 200 mg

1. Name of the Medical Product

Zydena®

2. Qualitative and Quantitative Composition

Zydena® Tablet (100 mg): 100 mg of Udenafil in one tablet (258 mg)

Zydena® Tablet (200 mg): 200 mg of Udenafil in one tablet (516 mg)

3. Pharmaceutical Form

Zydena® 100 mg Tablets are pale orange, film-coated oval tablets, marked 100 on one side and Z｜Y on the other.

Zydena® 200 mg Tablets are pale orange, film-coated oval tablets, marked 200 on one side and Z｜Y on the other.

4. Clinical Particulars

4.1 Therapeutic Indications

Zydena® is indicated for the treatment of erectile dysfunction.

4.2. Posology and Method of Administration

Zydena® tablets are for oral administration

Use in Adult males

For most patients, the recommended starting dose of Zydena® is 100 mg, taken orally approximately 30 minutes to 12 hours before sexual activity. Maximum recommended dosing frequency is once daily. Dosage may be increased to 200mg with caution after adverse reactions are closely examined at 100mg. Zydena® may be taken with or without food.

Use in Children

Zydena® is not indicated for use in newborns, children

Use in Elderly men

Elderly patients (over 65 years): Dose adjustment not necessary.

Use in Patients with Renal Impairment

Dose adjustment not necessary in male patients with mild renal impairment

Use in Patients with Hepatic Impairment

Dose adjustment not necessary for patients with mild hepatic impairment (Child-Pugh Class A)

4.3 Contraindications

Use of Zydena® is contraindicated in patients with known hypersensitivity to any component of the tablet.

Zydena® has been shown to potentiate the hypotensive effects of acute and chronic nitrates, and its co-administration with nitric oxide donors, organic nitrates or organic nitrites in any form, either regularly or intermittently, is therefore contraindicated. (see **4.4 Special warnings and precautions for use**).

Zydena® is contraindicated in patients with congenital QT prolongation syndrome, or who are on drugs that increase QT interval. Patients administering potent cytochrome P450 3A4 inhibitors (HIV protease inhibitor indinavir or ritonavir) are also contraindicated from Zydena®.

Zydena® is contraindicated in men for whom sexual activity is inadvisable due to underlying cardiovascular diseases (*e.g.* unstable angina or severe heart failure). (see **4.4 Special warnings and precautions for use**). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing Zydena®.

The safety of udenafil has not been studied in the following sub-groups of patients and therefore its use is contraindicated until further information is available: severe liver failure, renal failure, hypotension (blood pressure <90/50 mmHg), uncontrolled hypertension (blood pressure >170/100 mmHg), uncontrolled arrhythmias, stroke, myocardial infarction or a history of coronary artery bypass surgery within the last 6 months and known hereditary degenerative retinal disorders including retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

The efficacy and safety of combinations of Zydena® and other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Because Zydena® contains lactose, patients with genetic problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not administer Zydena®.

Patients under 18 years of age are contraindicated from using Zydena®.

Concomitant use of Zydena® and a Guanylate Cyclase (GC) stimulator (*e.g.* riociguat) is contraindicated, as PDE5 inhibitors, including Zydena®, may potentiate the hypotensive effects of GC stimulators.

4.4 Special Warnings and Precautions for Use

In order to diagnose the patient's erectile dysfunction and potential risks, patients should be examined and their medical history should be scrutinized. The use of Zydena® should be limited to patients in need of clinical treatment on the basis of these objective diagnoses.

Physicians should consider the cardiovascular status of their patients, since there is a potential cardiac risk associated with sexual activity. Treatments for erectile dysfunction, including Zydena®, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. Zydena® should not be used in patients who have had stroke, cerebral hemorrhage or myocardial infarction within the last six months, and when used in patients with a history of stroke, cerebral hemorrhage or myocardial infarction, the presence of cardiovascular disease should be examined sufficiently.

Physicians should advise patients to stop use of all PDE5 inhibitors, including Zydena®, and seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of permanent non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, that has been reported rarely in post-marketing surveillance studies in PDE5 inhibitors and has been shown to be potentially associated with the administration of PDE5 inhibitors. It is not possible to determine whether adverse reactions are directly related to the administration of PDE5 inhibitors or other factors. Physicians should also inform the patients that the use of vasodilators such as PDE5 inhibitors in patients who have already experienced NAION in one eye may increase the risk.

Physicians should advise patients to stop use of all PDE5 inhibitors, including Zydena®, and seek medical attention in the event of a sudden hearing loss or deafness, which may be accompanied by tinnitus and dizziness, in one or both ears.

Zydena® has been shown to have systemic vasodilatory properties that result in transient decreases in blood pressure. This is of little or no consequence in most patients. However,

prior to prescribing udenafil, 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, idiopathic hypertrophic subaortic stenosis), or those with severely impaired autonomic control of blood pressure. Moreover, as Zydena presents blood pressure lowering effects by its vasodilating action, it may augment the blood pressure lowering effect of nitrate or nitric oxide donor drugs.

In case of patients with renal impairment, Zydena® is not recommended for patients with moderate to severe renal impairment as the exposure of Zydena® (AUC) is increased and as there is limited clinical data. The safety and efficacy have not been studied in patients with renal failure.

Zydena® must be carefully administered in the professional judgment of the physician in patients with liver dysfunction (GOT, GPT more than three times the upper limit of normal) or renal impairment (serum creatinine > 2.5mg/dl). The safety and efficacy of Zydena® have not been studied in patients with liver failure or kidney failure.

Agents for the treatment of erectile dysfunction 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 anemia, multiple myeloma, or leukemia). In clinical trials, no cases of priapism or erection lasting longer than 4 hours were reported with Zydena®. However, erection lasting longer than 4 hours and priapism (painful erection lasting longer than 6 hours) have been rarely reported in PDE5 inhibitors. Patients who experience erection lasting longer than 4 hours should be instructed to seek immediate medical attention. If not treated, tissue damage and permanent loss of erection may occur. As Zydena® is neither an aphrodisiac nor stamina enhancer, it cannot be used for purposes other than the treatment of erectile dysfunction.

In patients administering CYP450 3A4 inhibitors (erythromycin, itraconazole, ketoconazole), increase of plasma concentration has been observed. Therefore, they should be used with caution such as initial dose adjustment. Patients with active gastroesophageal reflux disease (GERD) or hiatal hernia associated with reflux esophagitis or taking alpha-blockers (It has been reported that the concomitant use of PDE5 inhibitors with alpha-blockers has caused symptomatic hypotension in some patients) also should be careful when administered with Zydena®.

Zydena® has not been studied for the patients with uncontrolled diabetes, spinal cord injury, radical prostatectomy or radical pelvic surgery, low sexual desire, chemotherapy, and anticoagulants.
Patients with proliferative diabetic retinopathy should be administered with caution.

Zydena® contains Yellow No.5(Sunset Yellow FCF). It should be used with caution in patients who have hypersensitivity to or a history of allergic reaction to the ingredient.

As adverse effects such as dizziness, blurred vision have been reported in clinical trials, patients should be cautious when driving or operating the machinery.

4.5 Interaction with other medicinal products and other forms of interaction

1) Drugs that affect the serum concentration of Zydena®

- *in vitro* studies: Zydena® was metabolized principally by CYP450 3A4. Thus, CYP450 3A4 inhibitors may increase plasma concentration of Zydena®. In human, ketoconazole, itraconazole, ritonavir, indinavir, cimetidine, erythromycin and grapefruit juice are typical CYP450 3A4 inhibitors.
- *in vitro* studies: In healthy adults, the concomitant use of ketoconazole (400mg) with Zydena® (100mg) increased the AUC and C_{max} of Zydena® (100mg) approximately twice (212%) and approximately 0.8 times (85%), respectively, compared to the AUC and C_{max} of Zydena® (100mg) monotherapy.
- Although specific interaction has not been studied, when concomitantly used with inhibitors of CYP450 3A4 such as itraconazole, cimetidine, erythromycin, and grapefruit juice, the systemic exposure of Zydena® is expected to be increased. Therefore, it should be co-administered with caution.
- In PDE5 inhibitors, when co-administered with potent CYP450 3A4 inhibitors such as HIV protease inhibitors indinavir or ritonavir, a significant increase in systemic exposure of the drug has been reported. Therefore, co-administration is not recommended.
- In addition, CYP450 3A4 metabolism inducers such as dexamethasone, rifampicin and some antiepileptic drugs (phenytoin, phenobarbital, carbamazepine) promote the metabolism of Zydena®. Therefore, when co-administered, a decrease in plasma concentration of Zydena® is expected.
- When alcohol (0.6g/kg, mean maximum plasma concentration 0.088%) was co-administered with Zydena® (200mg), Zydena® did not augment the effects of alcohol

on blood pressure and heart rate, and the pharmacokinetics of the drug also did not change. However, because both Zydena® and alcohol has slight vasodilating effects, the blood pressure lowering effect may be augmented when administered in combination. Therefore, doctors should inform the patient that symptoms such as increased heart rate, decreased blood pressure, dizziness, headache and orthostatic symptoms may occur when a large amount of alcohol is co-administered with Zydena®.

- In a pharmacokinetic study of Zydena® 200mg and Dapoxetine 60mg co-administration in healthy subjects, the AUC was compared with the AUC of separate administration. The two drugs did not affect each other, and the C_{max} of Zydena® and Dapoxetine decreased by approximately 13.6% and 16.3%, respectively. Such changes of Zydena® were not considered clinically significant.

2) In an experiment with rats, nitroglycerin (2.5mg/kg, intravenous administration of a single dose) did not have a significant effect on the pharmacokinetics of Zydena® (30mg/kg, orally). However, because Zydena® has antihypertensive effects by vasodilatation, co-administration of nitroglycerin is not recommended.

3) In an experiment with rats, as amlodipine besylate (5mg/kg, orally for 3 days) has antihypertensive effects by vasodilation, the blood pressure may decrease due to amlodipine. Therefore, medical judgment is needed in concomitant use.

4) In a clinical study in which Zydena® (200mg) and selective alpha-1 blockers were concomitantly administered in 28 healthy adults, orthostatic systolic blood pressure, on average, was reduced by 4mmHg at most. With concomitant use, orthostatic systolic blood pressure was reduced to less than 85mmHg in four patients but without symptoms of hypotension. Although there has not been a clinical study on the concomitant use of Zydena® and alpha-blockers in patients, as Zydena® and alpha-blockers present equal vasodilating effects, patients should be warned about the possibility of a decrease in blood pressure.

   When administered in combination with alpha-blockers, PDE5 inhibitors including Zydena® may cause hypotension in some patients. Therefore, combination therapy of the two agents should be initiated at the minimum recommended doses in stable patients. Gradual increase of the alpha-blocker dosage may be associated with decreased blood pressure when administered with PDE5 inhibitors.

   Co-administration of PDE5 inhibitors and alpha-blockers may affect its safety by other factors such as a decrease in the amount of blood or anti-hypertensives.

5) In an experiment with rats, oral administration of omeprazole (30mg/kg) for about one

week followed by oral administration of Zydena® (30mg/kg) resulted in approximately 30% and 37% increase in the maximum plasma concentration and AUC, respectively.

6) The effect of Zydena® on other drugs
   In *in vitro* studies, Zydena® showed the IC50 of more than 200μM in all CYP450 isoform 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 except 2D6 (IC50 67.7μmol/L). Considering that the maximum plasma concentration of the drug was 2.2μmol/L after administration of the recommended dose, it is unlikely that Zydena® would affect the clearance rate of these isoforms.

4.6 Use in Pregnancy, Lactation, and Pediatrics

1) Zydena® is contraindicated in neonates, pediatrics, or women.
2) After administration of 300mg/kg/day to rats and 240mg/kg/day to rabbits during organogenesis, toxicity such as skeletal variations and delayed ossification of the fetus appeared. In pre- and post-natal development studies and maternal function tests in rats, when administered with 300mg/kg/day of Zydena®, stillbirths or hyposmia occurred.

4.7 Effect on Ability to Drive and Use Machines

In clinical trials, dizziness and blurred vision have been reported when treated with Zydena®. Therefore, patients should be cautious when driving or operating machinery.

4.8 Undesirable Effects

1) The following are adverse drug reactions that occurred in clinical trials of 923 patients where Zydena® 100mg or 200mg was administered on demand before sexual activity. In general, the adverse drug reactions were transient and their severity was mostly mild to moderate. The most common adverse drug reactions were headache and facial flushing.

≥10%	≥1%, <10%	≥0.1%, <1.0%
Cardiovascular: Flushing	Body as a Whole: Headache Sensory: Ocular hyperemia Respiratory: Nasal congestion Digestive: Dyspepsia	Body as a Whole: Chest pain, Abdominal pain, Fatigue, Hot flushes, Chest discomfort Nervous system: Dizziness, Nuchal rigidity, Paresthesia Sensory: Blurred vision, Ocular pain, Chromatopsia Skin and Appendages: Ocular swelling, Facial edema, Urticaria, Pruritus Digestive: Nausea, Toothache, Constipation, Gastritis, Gastric discomfort Metabolic and Endocrine: Excretory system disorder, Thirst Respiratory: Shortness of breath, Dry nose Musculoskeletal: Periarthritis

The following adverse reactions whose causality could not be excluded and that were not identified in pre-marketing clinical studies were reported in additionally conducted clinical trials - heaviness in head, feeling cold and drowsy, palpitation, orthostatic dizziness, lethargy, ear numbness, ocular discomfort, rash, erythema, vomiting, diarrhea, dyspnea with exercise, cough, epistaxis, erection increased and hypotension.

2) Patients have been administered up to 200mg once daily, and in this case, the type and frequency of adverse reactions significantly increased compared to 100mg..
3) Although not reported in clinical trials of Zydena®, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision,

has been reported rarely in post-marketing surveillance in temporal association with the use of phosphodiesterase type 5 (PDE5) inhibitors, including Zydena®. Most, but not all, of these patients had underlying anatomic or vascular risk factors for development of NAION, including but not necessarily limited to: low cup/disc ratio ("Crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia, and smoking. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors.

4) During post-marketing surveillance in patients taking PDE5 inhibitors including Zydena®, cases of sudden decrease or loss of hearing have been reported. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of Zydena®, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

5) Post-marketing surveillance study result of Zydena® 100mg and 200mg

   In the post-marketing surveillance study in 3,542 patients for 6 years for reexamination in Korea, the incidence of adverse reactions, regardless of causality, was 2.20% (78/3,542 patients) [90 cases], and the incidence of adverse drug reactions which the causal relationship with Zydena® could not be excluded was 2.03% (72/3,542 patients) [82 cases].

   - Reported adverse drug reactions were flushing 1.04% (37/3,542 patients) [39 cases], headache 0.76% (27/3,542 patients) [27 cases], dizziness 0.11% (4/3,542 patients) [4 cases], nasal congestion 0.11% (4/3,542 patients) [5 cases], dyspepsia, eye redness, 0.06% each (2/3,542 patients), [2 cases], visual disorders, gastroesophageal reflux (GERD), palpitations, 0.03% each (1/3,542 patients) [1 case]. Of these events, GERD was the unexpected adverse drug reaction.

4.9 Overdose

In single dose studies in healthy volunteers, when administered with up to 400mg of Zydena® once daily, no serious adverse reactions were observed. The adverse events (headache, facial flushing, etc.) showed an increase in frequency as the dosage increased, but most of them were minor reactions that were resolved without treatment. In case of an overdose, symptomatic therapy should be initiated in general. As Zydena® has a high plasma protein binding rate and is not excreted in urine, its clearance rate is not increased by dialysis.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Zydena® is an oral therapy for the treatment of erectile dysfunction, the fourth entrant to the global erectile dysfunction market and first by a Korean pharmaceutical company.
Zydena®, an oral therapy for erectile dysfunction, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) of the corpus cavernosum.

Mechanism of Action : The physiologic mechanism of erection of the penis involves release of nitric oxide(NO) in the corpus cavernosum and allowing inflow of blood.

NO activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth relaxation in the corpus cavernosum and allowing inflow of blood.

Udenafil 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

Udenafil at recommended dose has no effect in the absence of sexual stimulation.

Studies in vivo have shown that Udenafil is selective for PDE5.

Clinical studies

Zydena® demonstrated 88.5% improvement in patients with erectile dysfunction.
Based on the results from the phase III trial performed in 13 Korean centers for up to 6 months in duration, Zydena®, compared to placebo, showed 81.5% and 88.5% improvement in Global Assessment Questionnaire (GAQ) scores at doses of 100 and 200 mg, respectively, in 270 erectile dysfunction patients.

The efficacy and safety data of Zydena® were satisfactory in all of the phase I, II, and III trials performed in Korea.

Zydena® is a unique oral therapy for the treatment of erectile dysfunction, which has completed its entire clinical trial processes in Korea. The major adverse events are flushing, nasal congestion, headache, and dyspepsia. However, most adverse events were temporal and mild in severity, which soon resolved without treatment.

Zydena® does not inhibit phosphodiesterase type 11 (PDE11) (>3,000-fold selectivity) and adverse effects such as myalgia, back pain, and testicular toxicity, etc. have not been reported. Zydena® does not inhibit phosphodiesterase type 11 (PDE11) and adverse events such as myalgia, back pain, and testicular toxicity were not observed in clinical trials.

5.2 Pharmacokinetic Properties

Zydena® has an optimal duration of action of up to 8 to 12 hours.

Clinical pharmacokinetic study showed that the time to maximum concentration (Tmax) and half-life ($T_{1/2}$) of Zydena® are approximately 1 hour and 10 to 12 hours, respectively. The ability to maintain an erection sufficient for a successful intercourse (SEP3) at 8 to 12 hours after taking Zydena® (100 mg) was significantly superior to placebo in phase III trial. The duration of action was neither too short nor long, and was considered appropriate.

Pharmacokinetics in special patient groups:

Elderly

Zydena® (100mg) was administered once to 12 healthy elderly (age 65 to 80 years) and 12 young adults (age 19 to 45 years) in the pharmacokinetic properties and safety comparative evaluation clinical trial. The plasma peak concentration and AUC of Zydena® were 0.73 times and 0.88 times lower, respectively, in elderly patients compared to the young adults. Thus, as it is unlikely that the systemic exposure of Zydena® will be increased when used in the elderly, no dosage adjustment is necessary.

Renal Impairment

The pharmacokinetic characteristics and safety were compared and evaluated in a clinical trial where Zydena® 100 mg was administered for single therapy in 9 healthy male subjects, 9 patients with mild renal impairment (creatinine clearance rate 50~80 mL/min), 6 patients with moderate renal impairment (creatinine clearance rate 30~50 mL/min), and 7 patients with severe renal impairment (creatinine clearance rate < 30 mL/min). The exposure of Zydena®

(AUC) was increased compared to healthy male subjects by 1.3 times in case of mild renal impairment and approximately 1.6 times in case of moderate or severe renal impairment. Information on terminal stage renal failure patients undergoing dialysis is unknown.

Hepatic Impairment

The pharmacokinetic characteristics and safety were compared and evaluated in a clinical trial where Zydena® 100 mg was administered for single therapy in 6 healthy male subjects, 6 patients with mild hepatic impairment (Child-Pugh Class A) and 6 patients with moderate hepatic impairment (Child-Pugh Class B). The exposure of Zydena® (AUC) was increased compared to healthy male subjects by 1.05 times in case of mild hepatic impairment and 1.49 times in case of moderate hepatic impairment. There is no information on administering more than Zydena® 100 mg in patients with hepatic impairment.

6. Pharmaceutical Particulars

6.1 List of excipients

Each Zydena® tablet contains the following inactive ingredients:

Lactose, Corn starch, Light anhydrous silicic acid, Low substituted hydroxypropyl cellulose, Hydroxypropyl cellulose, Talc, Magnesium stearate, Hydroxypropyl methyl cellulose 2910, Titanium oxide, Al lake yellow 5.

6.2 Shelf Life

36 months

6.3 Special Precautions for Storage

Store Zydena below 30℃

6.4 Nature and Contents of Container

Zydena tablets are presented in blister packs of 2 tablets or 4 tablets per box

1) Please carefully read all information on the leaflet before taking this medicine and keep this leaflet.
2) To prevent misuse and guarantee quality, do not store in a different container.

6.5 Special Precautions for Disposal

1) Keep out of reach and sight of children
2) Keep the drug in the original package as transferring the drug into other containers may cause accidents and is not desirable in terms of maintaining the quality of the drug.

7. Date of revision of the text

Date of Revision: 2024.03

The Creation date for the 1st version: 2009. 05

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