Udenafil tablets
100 mg and 200 mg

zydena®

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FZYT-7J005

Presentation

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.
In addition to udenafil, each ZYDENA tablet contains the following inactive ingredients: lactose, corn starch, light anhydrous silicis acid, low substituted hydroxypropyl cellulose, hydroxypropyl cellulose, talc, magnesium stearate, hydroxypropyl methyl cellulose 2910, titanium dioxide, al lake yellow 5.
ZYDENA tablets are presented in blister packs of 2 tablets or 4 tablets per box.

Pharmacology

ZYDENA, an oral therapy for the treatment of erectile dysfunction (ED), is a pyrazolopyrimidinone class and a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) of the corpus cavernosum, which induce potent penile erection.
ZYDENA demonstrated 88.5% improvement in patients with ED. Based on the results from the phase III trial performed in 13 Korean centers, involving 270 ED patients, ZYDENA showed 81.5% and 88.5% improvement in Global Assessment Questionnaire (GAQ) scores at doses of 100 and 200 mg, respectively, compared to placebo.
ZYDENA has an optimal duration of action of up to 8-12 hours. Clinical pharmacodynamic study showed that the time to maximum concentration (Tmax) and half-life (TI/2) of ZYDENA are approximately 1 hour and 10-12 hours, respectively. The ability to maintain an erection sufficient for a successful intercourse (SEP3) at 8-12 hours after taking ZYDENA (100 mg) was significantly superior to placebo in phase III study.
The efficacy and safety of ZYDENA are satisfactory in all the phase I, II, and III studies. ZYDENA is an oral therapy for the treatment of ED, which completed the 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.
Moreover, these adverse events soon resolved without treatment.
ZYDENA does not inhibit phosphodiesterase type 11 (PDE11) (>3,000- fold selectivity) and adverse effects such as myalgia, back pain have not been reported.
Geriatric Use: When udenafil (100 mg) was given to 12 healthy elderly volunteers (65-80 years) and 12 healthy younger volunteers (19-45 years), AUC and Cmax of udenafil (l00 mg) in the elderly group were lower by 0.73-fold and 0.88-fold, respectively, compared to that of the younger group. Therefore, as the possibility of increased udenafil exposure in the elderly patients is rare, dose control is not required with elderly patients.
Administration experience in patients with renal impairment
The pharmacokinetic characteristics and safety was compared and evaluated in a clinical trial where ZYDENA 100mg was administered for single therapy in 9 healthy male subjects, 9 patients with mild renal impairment (creatinine clearance rate 50~80mL/min), 6 patients with moderate renal impairment (creatinine clearance rate 30~50mL/min), and 7 patients with severe renal impairment (creatinine clearance rate < 30mL/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.
Administration experience in patients with hepatic impairment
The pharmacokinetic characteristics and safety was compared and evaluated in a clinical trial where ZYDENA 100mg 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 100mg in patients with hepatic impairment.

Indication

ZYDENA is indicated for the treatment of erectile dysfunction.

Dosage and Administration

For most patients, the recommended starting dose of ZYDENA in male adults is 100 mg, taken orally approximately 30 minutes to 12 hours before sexual activity. The maximum recommended dosing frequency is once per day. The dose may be increased to 200 mg, based on the careful consideration of individual effectiveness and toleration including adverse reactions to 100 mg. This drug can be taken without regard to meals. Elderly patients (over 65 years): dose control is not required in elderly patients.

Contraindications

Patients with severe liver failure or renal failure
Patients under 18 years of age
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 simulators
Use of ZYDENA is contraindicated in patients with known hypersensitivity to any component of the tablet.
ZYDENA was 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.
Drugs which must not be used concomitantly include glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. (see Warnings and Precautions).
ZYDENA is contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors (e.g. patients with severe cardiovascular disease such as established cardiac failure and unstable angina pectoris) (see Warnings and Precautions). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing ZYDENA.
ZYDENA is not recommended in patients with male erectile dysfunction with a previous episode of non-arteritic anterior is chemic optic neuropathy (NAION) (see Warnings and Precautions).
The safety of udenafil has not been studied in the following sub-groups of patients and its use is therefore contraindicated until further information is available: severe hepatic impairment, hypotension (blood pressure <90/50 mmHg), hypertension (blood pressure >170/110 mmHg), recent history of stroke cerebral hemorrhage or myocardial infarction and known hereditary degenerative retinal disorders such as 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. Patients with congenital QT prolongation syndrome, or who are on drugs that increase the QT interval. Because this medicine contains lactose, patients with genetic problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not administer this drug.

Warnings and Precautions

A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.
Physicians should consider the cardiovascular status of their patients, since there is a potential for 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.
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 non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, which has been rarely reported in post-marketing surveillance (PMS) of PDE5 inhibitors, except ZYDENA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE5 inhibitors (see Contraindications).
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, hypertrophic obstructive cardiomyopathy), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.
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 anaemia, multiple myeloma or leukemia).
As ZYDENA is neither an aphrodisiac drug nor a sexual stimulant, it should be used only for the treatment of erectile dysfunction.
ZYDENA has not been studied for the patients with spinal cord injury, adical prostatectomy, hyposexual desire, anticancer medication, and anticoagulant medication.
As adverse effects such as dizziness, blurred vision were reported in clinical trials, patients should be careful when driving and operatingmachinery.

Pregnancy, Nursing Mothers, and Pediatric Use

ZYDENA is not indicated for use in newborns, children, or women.
In the embryo fetal development study performed in rats and rabbits,only high doses of udenafil (300 mg/kg/day and 240 mg/kg/day) showed skeletal variations and ossific retardations in fetuses. In the study for the effects of udenafil on preand postnatal development, including maternal function, carried out in rats by oral administration, stillbirth or ateliosis of offsprings were noted at the dose of 300 mg/kg/day.

Adverse Reactions

ZYDENA was administered to 923 patients during Korean nationwide clinical trials. In general, most adverse events were temporal and its severity was mild to moderate. The most common adverse events were flushing and headache.

The following adverse events were reported in clinical trials:

Body System	Percentage		
	≥ 10%	1% - 10%	0.1% - 1%
Cardiovascular	Flushing		
General		Headache	Chest Pain, Abdominal Pain, Fatigue, Feeling Hot, Chest Discomfort
Nervous system			Dizziness, Nuchal Rigidity, Paraesthesia
Sensory		Percentage	Blurred Vision, Eye Pain, Chromatopia
Skin and Appendages			Eyelid Edema, Face Edema, Urticaria Pruritus
Gastrointestinal			Dyspepsia Nausea, Toothache, Constipation, Gastritis, Stomach Discomfort
Metabolic and Endocrine			Thirst, Abnormal lacrimation
Respiratory		Nasal Congestion	Dyspnea, Nasal Dryness
Musculoskeletal			Periarthritis

In additional clinical studies, drug related adverse events unconfirmed before marketing are head discomfort, feeling cold, feeling dim, palpitation, postural dizziness, somnosis, ear daze, eye discomfort, rash, erythema, diarrhea, dyspnea, respiratory distress in exercise, cough, nasal hemorrhage, increase erection, and hypotension.

In clinical trials of single doses up to 200 mg per day, the types of adverse events and incidence rates were significantly increased from those seen at 100 mg dose level.

Not reported in the clinical studies, 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 (PMS) studies of PDE5 inhibitors. Most, but not all, of these patients had underlying anatomic or vascular risk factors for developing NAION, including but not necessarily limited to: low cup to 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.

A sudden hearing loss or deafness in one or both ears, which might be in temporal association with the use of PDE5 inhibitors, has been rarely reported in post-marketing surveillance (PMS). Even though, it is reported that the disease status and other factors will be related to adverse events about hearing in a few cases, medical tracing data which can be aware of that relationship are not confirmed in major cases. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient's underlying deafness risk factors, to a combination of these factors, or to other factors.

Interaction

1) Effects of other drugs on the plasma concentration of ZYDENA:
   - In vitro studies; Udenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4. Therefore, inhibitors of these enzymes are expected to increase the plasma concentration of udenafil. In human, ketoconazole, itraconazole, ritonavir, indinavir, cimetidine, erythromycin, and grapefruit juice are representative CYP450 3A4 inhibitors.
   - In vivo studies; Ketoconazole (400 mg) induced 212% and 85% increase in AUC and Cmax of udenafil, respectively, when coadministered with ZYDENA (100 mg) to healthy volunteers.
   - Even though the interaction studies have not been studied, the coadministration with other CYP450 3A4 inhibitors such as itraconazole, cimetidine, erythromycin, and grapefruit juice are expected to increase plasma concentration of udenafil, therefore careful consideration is needed.
   - The coadministration with HIV protease inhibitors ritonavir or indinavir, potent CYP450 3A4 inhibitors, results in a significant increase in plasma udenafil concentration. Therefore, the coadministration is not recommended.
   - Moreover, CYP450 3A4 inducers such as dexamethasone, rafampin, and anticonvulsants (carbamazepine, phenytoin, and phenobarbital) can accelerate udenafil metabolism. Therefore the co-administration affects to decrease plasma concentration of udenafil.
   - The coadministration of udenafil (200 mg) with alcohol (0.6 g/kg, mean maximum blood alcohol levels of 0.088%) did not potentiate the effect of alcohol on blood pressure and heart rate. The pharmacokinetics of udenafil was not affected by alcohol. However, physicians should inform patients of the possible symptoms, such as increased heart rate, decreased blood pressure, dizziness, myalgia, and orthostatic syndrome, as both udenafil and alcohol have mild vasodilatory properties.
2) When udenafil (30 mg/kg, p.o.) was coadministered with nitroglycerine (2.5 mg/kg, i.v.) to rats, the pharmacokinetics of udenafil was not affected.
   However, due to the blood-pressure-lowering effect of nitroglycerine, the concomitant use is not recommended.
3) When amlodipine besylate (5 mg/kg, 3 days, p.o.) was administered to rats, the blood pressure was significantly lowered. Therefore, the concomitant use with udenafil requires careful consideration.
4) When ZYDENA (200 mg) was given simultaneously with 0.4 mg of tamsulosin to healthy volunteers, the mean standing systolic blood pressure was decreased by 4 mmHg (maximum). Although 4 out of 28 subjects temporarily experienced a standing systolic blood pressure of lower than 85 mmHg, no subjects showed symptomatic hypotension. ZYDENA and alphablockers have not been evaluated to determine whether they can be safely administered together. However, as these two classes of drugs both act as vasodilators with blood-pressure-lowering effects, patients must be warned.
   In some patients, concomitant use of alpha-blockers and PDE5 inhibitors including ZYDENA, may lead to symptomatic hypotension so, coadministration should be initiated at the lowest dose only when the patients are stable on either alpha-blockers or PDE5 inhibitor. Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by variables including hypovolemia and other anti-hypertensive drugs.
5) When ZYDENA (30 mg/kg) was administered to rats after a week administration of omeprazole (30 mg/kg), Cmax and AUC of udenafil were increased by approximately 30% and 37%, respectively.
6) Effects of ZYDENA on other drugs: Udenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 (IC50> 200 μM, except IC50 = 67.7 for 2D6). Given udenafil peak plasma concentrations of approximately 2.2 μM after recommended doses, it is unlikely that ZYDENA will alter the clearance of substrates of these isozymes.

Overdose

In studies with healthy volunteers of single doses up to 400 mg, no severe adverse events were observed. The frequency of adverse events (headache, flushing) increased with dose, but most adverse events were mild in severity and soon resolved without treatment. In cases of overdose, standard supportive measures should be adopted as required.

Renal dialysis is not expected to accelerate clearance as udenafil is highly bound to plasma proteins and it is not eliminated in the urine.

Storage Condition

1. Caution of Store and Handling
   - Keep ZYDENA out of the reach and sight of children
   - To prevent accidents and guarantee quality, do not store in a different container.
   - Please carefully read the leaflet before taking this medicine and keep this leaflet
2. Storage

Tight container, Store ZYDENA below 30℃

ZYDENA® (Udenafil) is a registered trademark of Dong-A ST Co., Ltd.

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This leaflet was created in September, 2017

FZYT-7J005

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