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ASSURANS Tablets (Sildenafil citrate)

Composition

Each film-coated tablet contains:
Sildenafil Citrate IP
equivalent to Sildenafil ..... 20 mg
Colour: Titanium Dioxide IP

Dosage Form/s

Tablets

Pharmacology

Pharmacodynamics

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary arterial hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation in the systemic circulation. Single and chronic doses of sildenafil may cause mild and transient decreases in supine blood pressure. However, greater effects were seen amongst patients receiving concomitant nitrates.
Studies in vitro have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to colour vision observed with higher doses or plasma levels.
In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues, including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed in vitro, and the mild peripheral arterial-venous dilatation in vivo.

Pharmacokinetics

Absorption and Distribution: Sildenafil is rapidly absorbed after oral administration, with a mean absolute bioavailability of about 41%. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When sildenafil is taken with a high-fat meal, 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%. The mean steady-state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into

the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.
Bioequivalence was established between the 20 mg tablet and the 10 mg/mL oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).
Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours.
After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).
The concomitant use of potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil. After either oral or intravenous administration, sildenafil is excreted as metabolites, predominantly in the faeces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

▶ Pharmacokinetics

Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in patients with PAH. The dataset available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a significant impact on sildenafil pharmacokinetics in patients with PAH.
In patients with PAH, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of C_{min} levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with PAH compared to healthy volunteers.
Hepatic Insufficiency: In volunteers with mild to moderate hepatic cirrhosis (Child-Pugh class 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. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.
Geriatric Patients: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 84% and 107% higher plasma concentrations of sildenafil and its active N-desmethyl metabolite, respectively, compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in the AUC of free (unbound) sildenafil and its active N-desmethyl metabolite were 45% and 57%, respectively.
Renal Impairment: In volunteers with mild (CLcr = 50-80 mL/min) and moderate (CLcr = 30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) was not altered. In volunteers with severe (CLcr less than 30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and Cmax compared to age-matched volunteers with no renal impairment. In addition, N-desmethyl metabolite AUC and Cmax values were significantly increased 200 % and 79 %,

respectively, in subjects with severe renal impairment compared to subjects with normal renal function.

Indications

ASSURANS tablets is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when sildenafil was added to background epoprostenol therapy.
Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Dosage And Administration

The recommended dose of sildenafil is 20 mg three times a day (t.i.d.). ASSURANS tablets should be taken approximately 4-6 hours apart, with or without food. Treatment with doses higher than 20 mg t.i.d. is not recommended. In the clinical trial no greater efficacy was achieved with the use of higher doses.

Contraindications

Consistent with its known effects on the nitric oxide/cGMP pathway, sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.
Combination with the most potent of the CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir).
The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.
Sildenafil is contraindicated in patients with a known hypersensitivity, including anaphylactic reaction, shock and anaphylactoid reaction to any component of the tablet. 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.
Hypersensitivity, including anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, has been reported in association with the use of sildenafil.
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

Warnings And Precautions

Pediatric Use
In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing sildenafil dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of sildenafil, particularly chronic use, is not recommended in children.
Hypotension
Sildenafil has vasodilatory properties, resulting in mild and transient decreases in blood pressure. Prior to prescribing sildenafil to their patients,physicians should carefully consider whether those with certain underlying conditions could be adversely affected by such vasodilatory effects, e.g., patients with resting

hypotension (BP <90/50), or with fluid depletion, severe left ventricular outflow obstruction, or autonomic dysfunction. Monitor blood pressure when co-administering blood pressure lowering drugs with Sildenafil.

Worsening Pulmonary Vascular Occlusive Disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of sildenafil to patients with veno-occlusive disease, administration of sildenafil to such patients is not recommended. Should signs of pulmonary oedema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

Alpha-blockers

Caution is advised when phosphodiesterase type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including sildenafil, 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. In the sildenafil interaction studies with alpha-blockers, cases of symptomatic hypotension consisting of dizziness and lightheadedness were reported. No cases of syncope or fainting were reported during these interaction studies. Consideration should be given to the fact that safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and concomitant use of anti-hypertensive drugs.

Cardiovascular risk factors

In post-marketing experience with sildenafil for male erectile dysfunction, serious cardiovascular events, including myocardial infarction, unstable angina, sudden cardiac death, ventricular arrhythmia, cerebrovascular haemorrhage, transient ischaemic attack, hypertension and hypotension have been reported 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.

Caution is advised in patients with coronary artery disease causing unstable angina and hypertension (BP >170/110) treated with sildenafil.

Priapism

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). In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism (painful erection greater than 6 hours in duration) is not treated immediately, penile tissue damage and permanent loss of potency could result.

Epistaxis

The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonists (9% versus 2% in those not treated with concomitant vitamin K antagonists).

The safety of sildenafil is unknown in patients with bleeding disorders or active peptic ulceration.

Bleeding disorders

Studies with human platelets indicate that sildenafil potentiates the anti-aggregatory 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.

Vaso occlusive crises in patients with sickle cell anaemia

In a small, prematurely terminated study of patients with pulmonary hypertension (PH) secondary to sickle cell disease, vaso-occlusive crises requiring hospitalization were more commonly reported by patients who received sildenafil than by those randomized to placebo. The effectiveness of sildenafil in PH secondary to sickle cell anemia has not been established.

Retinitis pigmentosa

The safety of sildenafil has not been studied in patients with known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases) and therefore its use is not recommended.

Visual events

When used to treat erectile dysfunction, non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision, has been reported postmarketing in temporal association with the use of phosphodiesterase type 5 (PDE-5) inhibitors, including sildenafil. 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. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged 50 per year in the general population. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, to the patient's underlying vascular risk factors or anatomical defects, to a combination of these factors, or to other factors. Advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes while taking PDE-5 inhibitors, including sildenafil. Physicians should also discuss the increased risk of NAION with patients who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators, such as PDE-5 inhibitors.

There are no controlled clinical data on the safety or efficacy of sildenafil in patients with retinitis pigmentosa, a minority whom have genetic disorders of retinal phosphodiesterases. Prescribe sildenafil with caution in these patients. The patient should be advised that in case of sudden visual defect, he should stop taking sildenafil and consult a physician immediately.

Hearing Loss

Cases of sudden decrease or loss of hearing, which may be accompanied by tinnitus and dizziness, have been reported in temporal association with the use of PDE-5 inhibitors, including sildenafil. In some of the cases, medical conditions and other factors were reported that may have played a role. 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 sildenafil, to the patient's underlying risk factors for hearing loss, a combination of these factors, or to other factors.

Advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE-5 inhibitors, including sildenafil.

Vitamin K antagonists

In pulmonary arterial hypertension patients, there may be a potential for increased risk of bleeding when sildenafil is initiated in patients already using a Vitamin K antagonist, particularly in patients with pulmonary arterial hypertension secondary to connective tissue disease.

Effects on ability to drive and use machines

Sildenafil has moderate influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they might be affected by sildenafil, before driving or using machines.
Combination with other PDE-5 inhibitors
Sildenafil is also marketed as VIAGRA®. The safety and efficacy of combinations of ASSURANS with VIAGRA or other PDE-5 inhibitors have not been studied. Inform patients taking sildenafil not to take VIAGRA or other PDE5 inhibitors.

▶ Drug Interactions

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 clearance.
In vivo studies
Co-administration of oral sildenafil and intravenous epoprostenol has been evaluated. The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg, bosentan, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration. There is a pharmacokinetic interaction between sildenafil and bosentan.
The safety and efficacy of sildenafil when co-administered with other PDE5 inhibitors has not been studied in pulmonary arterial hypertension patients. Population pharmacokinetic analysis of pulmonary arterial hypertension clinical trial data indicated a reduction in sildenafil clearance and/or an increase of oral bioavailability when co-administered with CYP3A4 substrates and the combination of CYP3A4 substrates and beta-blockers. These were the only factors with a statistically significant impact on sildenafil pharmacokinetics in patients with pulmonary arterial hypertension. The exposure to sildenafil in patients on CYP3A4 substrates and CYP3A4 substrates plus beta-blockers was 43 % and 66 % higher, respectively, compared to patients not receiving these classes of medicines. Sildenafil exposure was 5-fold higher at a dose of 80 mg three times a day compared to the exposure at a dose of 20 mg three times a day. This concentration range covers the increase in sildenafil exposure observed in specifically designed drug interaction studies with CYP3A4 inhibitors (except with the most potent of the CYP3A4 inhibitors eg, ketoconazole, itraconazole, ritonavir).
CYP3A4 inducers seemed to have a substantial impact on the pharmacokinetics of sildenafil in pulmonary arterial hypertension patients, which was confirmed in the in-vivo interaction study with CYP3A4 inducer bosentan.
Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. Caution is recommended in case of co-administration. Efficacy of sildenafil should be closely monitored in patients using concomitant potent CYP3A4 inducers, such as carbamazepine, phenytoin, phenobarbital, St John's wort and rifampicine.
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. Based on these pharmacokinetic results co-administration of sildenafil with ritonavir is contraindicated in

pulmonary arterial hypertension patients. 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.
When a single 100 mg dose of sildenafil was administered with erythromycin, a specific 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. No dose adjustment is required. 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. No dose adjustment is required. The most potent of the CYP3A4 inhibitors such as ketoconazole and itraconazole would be expected to have effects similar to ritonavir. CYP3A4 inhibitors like clarithromycin, telithromycin and nefazodone are expected to have an effect in between that of ritonavir and CYP3A4 inhibitors like saquinavir or erythromycin, a seven-fold increase in exposure is assumed.
Therefore, dose adjustments are recommended when using CYP3A4 inhibitors. The population pharmacokinetic analysis in pulmonary arterial hypertension patients suggested that co-administration of beta-blockers in combination with CYP3A4 substrates might result in an additional increase in sildenafil exposure compared with administration of CYP3A4 substrates alone. Grapefruit juice is a weak inhibitor of CYP3A4 gut wall metabolism and may give rise to modest increases in plasma levels of sildenafil. No dose adjustment is required but the concomitant use of sildenafil and grapefruit juice is not recommended.
Single doses of antacid (magnesium hydroxide/aluminium hydroxide) did not affect the bioavailability of sildenafil. Co-administration of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg) did not affect the pharmacokinetics of sildenafil. Nicorandil is a hybrid of potassium channel activator and nitrate. Due to the nitrate component it has the potential to have 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 (IC50 > 150 µM). There are no data on the interaction of sildenafil and non-specific phosphodiesterase inhibitors such as theophylline or dipyridamole.
In vivo studies
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 had no significant effect on atorvastatin exposure (AUC increased 11 %), suggesting that sildenafil does not have a clinically relevant effect on CYP3A4. No interactions were observed between sildenafil (100 mg single dose) and acenocoumarol.
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.
In a study of healthy volunteers sildenafil at steady state (80 mg three times a day) resulted in a 50 % increase in bosentan AUC (125 mg twice daily). Caution is recommended in case of co-administration. 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.
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 systolic and diastolic blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, respectively, 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. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals.
Sildenafil (100 mg single dose) did not affect the steady state pharmacokinetics of the HIV protease inhibitor saquinavir, which is a CYP3A4 substrate/inhibitor. 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.
Riociguat: Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has been shown to augment the hypotensive effects of PDE5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including sildenafil, is contraindicated.
Sildenafil had no clinically significant impact on the plasma levels of oral contraceptives (ethinyloestradiol 30 µg and levonorgestrel 150 µg).
Paediatric population: Interaction studies have only been performed in adults.

▶ Renal Impairment

No dose adjustments are required for renal impaired patients (including severe renal impairment, creatinine clearance <30 mL).

▶ Hepatic Impairment

Initial dose adjustments are not required in patients with hepatic impairment (Child-Pugh class A and B). A downward dose adjustment to 20 mg twice daily should be considered after a careful benefit-risk assessment only if therapy is not well-tolerated.
Sildenafil is contraindicated in patients with severe hepatic impairment (Child-Pugh class C).

▶ Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies of sildenafil in pregnant women. Because animal reproduction studies are not always predictive of human response, sildenafil should be used during pregnancy only if clearly needed.

▶ Lactation

It is not known if sildenafil citrate and/or metabolites are excreted in human breast milk. Sildenafil should not be administered to breast-feeding mothers.

▶ Paediatric Use

In the long term paediatric extension study, an increase in deaths was observed in patients administered doses higher than the recommended dose. Therefore, doses higher than the recommended doses should not be used in paediatric patients with PAH. Use of Sildenafil, particularly chronic use, is not recommended in children.

▶ Geriatric Use

Clinical studies of sildenafil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Undesirable Effects

The following serious adverse events are discussed elsewhere in the labeling:

- Mortality with pediatric use
- Hypotension
- Vision loss
- Hearing loss
- Priapism
- Vaso-occlusive crisis

Sildenafil is generally well tolerated. The most common effects seen were headache, dyspepsia, flushing, insomnia, epistaxis, erythema, dyspnea, exacerbated, rhinitis, diarrhoea, myalgia, pyrexia, gastric disturbances, sinusitis, and paraesthesia. At higher doses than recommended, there was a greater incidence of the above-mentioned adverse events. Visual disturbances were identified as mild and transient, and were, predominantly, colour-tinge to vision, but there was also increased sensitivity to light, or blurred vision. Cases of eye and retinal haemorrhage have been reported in less than 2% of patients at the recommended sildenafil doses.

▶ Post Marketing Experience:

Cardiovascular Events

In postmarketing experience with sildenafil at doses indicated for erectile dysfunction, serious cardiovascular, cerebrovascular, and vascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack, hypertension, pulmonary hemorrhage, and subarachnoid and intracerebral hemorrhages have been reported in temporal association with the use of the drug. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after use concurrent with sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient’s underlying cardiovascular disease, or to a combination of these or other factors.

Nervous system Seizure, seizure recurrence

Ophthalmologic NAION

If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects you can help provide more information on the safety of this product.

Overdosage

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen

at lower doses but the rates 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 is not eliminated in the urine.

Storage And Handling Instructions

Store below 30°C. Protect from moisture.

Packaging Information

ASSURANS is available in Blister of 10 tablets
Last updated: *October 2017*
Last reviewed: *June 2018*

ASSURANS Tablets
