Patient information

Important safety information

SEGUREX® 50

Sildenafil

POM

SEGUREX® contains sildenafil. **THIS IS A PRESCRIPTION MEDICINE THAT MUST BE USED ONLY UNDER A DOCTOR'S CARE.**

Take SEGUREX® (sildenafil) exactly as prescribed by your doctor; this is the only way to obtain the efficacy and the safety levels reported in the world literature.

Before you start taking sildenafil, your doctor should assess and discuss with you the potential cardiac risk associated with sexual activity.

YOU SHOULD NOT TAKE SEGUREX® (sildenafil) if you are using -either regularly and/or intermittently- or if you intend to use **ORGANIC NITRATES** in any form (sublingual tablets, extended-release tablets, capsules, tablets, sprays, skin patches or discs, intravenous solutions) and/or any other medicines that lead to the formation of NITRIC OXIDE.

THE CONCOMITANT USE OF SILDENAFIL WITH ORGANIC NITRATES ENTAILS THE RISK OF SEVERE HYPOTENSION.

Nitrates can be found in many medicines and drugs, such as:

- isosorbide mononitrate
- isosorbide dinitrate
- nitroglycerine
- sodium nitroprusside
- amyl nitrite
- erythrityl tetranitrate

How should you take SEGUREX®?

Take SEGUREX® exactly as prescribed by your doctor, one hour before sexual activity. Do not take more SEGUREX® than your doctor prescribes. **SEGUREX® SHOULD NOT BE TAKEN MORE THAN ONCE A DAY.**

Further information may be obtained from the leaflet enclosed in the package.

ASK YOUR DOCTOR IF YOU HAVE ANY QUESTIONS OR IF YOU WANT TO KNOW MORE ABOUT SEGUREX®.

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Devoted to People's Health

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Lebanon Reg. № 24.529
Last revised:October 5, 2006

Material Reciclable

SEGUREX®
SILDENAFIL 50 mg

POM
Made in Argentina

Coated tablets

DESCRIPTION

Each coated tablet contains:
Sildenafil (as citrate 70,22 mg)..... 50 mg
Excipients (Dibasic calcium phosphate, Pregelatinized starch, Microcrystalline cellulose, Croscarmellose sodium, Colloidal silicon dioxide, Corn starch, Magnesium stearate, Hydroxypropylmethylcellulose, Propylene glycol, Titanium dioxide, Tale, Indigotine aluminum lake [FD&C Blue No. 2], Brilliant blue FCF aluminum lake [FD&C Blue No. 1])

MECHANISM OF ACTION

Sildenafil increases the efficacy of the physiologic mechanism of erection of the penis in the presence of sexual stimulation.

In patients with organic or psychogenic erectile dysfunction, sexual stimulation results in improved erections alter sildenafil administration. The efficacy is greatest approximately 1 hour post administration. Sildenafil is effective in a broad range of patients with erectile dysfunction, including those with cardiovascular disease, coronary artery bypass graft, diabetes mellitus, depression, radical prostatectomy, transurethral resection of the prostate and spinal cord injury, and in patients taking antidepressants or antipsychotics.

INDICATIONS AND USAGE

Sildenafil is indicated for the oral treatment of erectile dysfunction in men.

CLINICAL PHARMACOLOGY

Sildenafil is a selective inhibitor of cyclic guanosine monophosphate (cyclic GMP)-specific phosphodiesterase type 5 (PDE5).

Penile erection involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. By activating the enzyme guanylate cyclase, NO stimulates the synthesis of cyclic guanosine monophosphate (cGMP). This triggers smooth muscle relaxation, allowing increased blood flow into the corpus cavernosum.

Inhibition of PDE5 by sildenafil prevents the degradation of cGMP, and therefore results in higher intracellular levels of this messenger. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Sildenafil is highly selective for PDE5; its effect is more potent on PDE5 than on other known phosphodiesterases. This selectivity profile is important because sildenafil has no effect on in vitro cardiac contractility or on the electrocardiograms of healthy male volunteers. The lower selectivity for PDE6, an enzyme found principally in the retina, is thought to account for certain visual abnormalities (such as photophobia or color tinge to vision) observed with higher doses.

PHARMACOKINETICS

Sildenafil is rapidly absorbed alter oral administration in the fasted state; maximum plasma concentrations are reached within 30-120 minutes (mean 60 minutes) of dosing. When sildenafil is taken with a high-fat meal, the time to reach peak plasma concentration may be delayed 60 minutes. Sildenafil is widely distributed into the tissues (volume of distribution: 105 L). Both sildenafil and its major circulating metabolite, N-desmethyl sildenafil, are mostly bound to plasma proteins (>95%). Plasma concentrations of this metabolite are approximately 40% of !hose observed for sildenafil. Only a minimal proportion of the administered dose of sildenafil (1/10.000) may appear in the semen of patients 90 minutes alter dosing. The ter minal half-life is about 4 hours.

Sildenafil is metabolized predominantly by the CYP3A4 (major route) and by the CYP2C9 (minor route) hepatic microsomal isoenzymes. N-desmethyl sildenafil has an activity profile similar to that of sildenafil and hall the potency of the parent drug. Both are excreted mostly in the feces and to a lesser extent in the urine (80% and 13% of the administered oral dose, respectively). In the following cases, plasma levels of sildenafil may be greater than !hose seen in healthy control volunteers: healthy elderly men (65 years or over; 40% increase), patients with severe renal impairment (creatinine clearance <30 ml/min; 100% increase) and patients with hepatic cirrhosis (80% increase).

DOSAGE AND ADMINISTRATION

The mean recommended dose for most patients is 50 mg, taken approximately 1 hour before sexual activity. In certain cases, sildenafil may be taken 4 hours to Y2 hour before sexual activity. In patients aged >65 years, in patients with severe renal impairment (creatinine clearance <30 ml/min) and in patients with cirrhosis, the starting dose should be the hall of the recommended dose.

CONTRAINDICATIONS

SEGUREX® is contraindicated in patients with a known hypersensitivity to sildenafil or any other component of the tablet, and in patients who are using organic nitrates or nitric oxide donors.

After patients have taken sildenafil, it is unknown when nitrates, if necessary, may be safely administered.

Special caution is advised in the following patients: age >65, hepatic impairment (cirrhosis), severe renal impairment (creatinine clearance <30 mL/min), and concomitant use of potent cytochrome P450 3A4 inhibitors (erythromycin, ketoconazole, itraconazole), since the pharmacokinetic parameters and plasma levels of sildenafil at 24 hours post dose in such patients were 3 to 8 times higher than those seen in healthy volunteers.

WARNINGS

Sildenafil may potentiate the hypotensive effects of nitrates, so it should not be administered to patients who are using nitrates. (See Interactions)

Non-arteritic anterior ischemic optic neuropathy (NAION): Decreased vision and vision loss due to NAION have been reported rarely with the use of sildenafil. Most of these patients had risk factors for NAION such as low cup to disc ratio ("crowded disc"), age >50, hypertension, coronary artery disease, hyperlipidemia and smoking. It has not yet been determined whether there is a causal relationship between the use of PDE5 inhibitors and NAION. Physicians should inform patients about the increased risk of NAION in individuals with underlying risk factors and advise them to stop use of all PDE5 inhibitors, including sildenafil, and seek medical assistance if they experience sudden loss of vision in one or both eyes.

Cardiac risk of sexual activity: sildenafil should not be used in patients for whom sexual activity is in· advisable due to their underlying cardiovascular status.

Vasodilatory effects: sildenafil has systemic vasodilatory effects, resulting in transient decreases in blood pressure. Normally, this is of little consequence for most patients; however, patients with cardiovascular disease may be adversely affected these vasodilatory effects, especially if combined with sexual activity.

Patients not studied in clinical trials: the following groups have not been studied in controlled clinical trials on the safety or efficacy of sildenafil; therefore, if prescribed, extreme caution should be exercised:

a) **Patients who have suffered a myocardial infarction, stroke or life-threatening arrhythmia within the last 6 months.**

b) **Patients with hypotension (blood pressure <90/50 mm Hg) or hypertension (blood pressure >170/100 mm Hg).**

c) **Patients with a history of cardiac failure or coronary artery disease causing unstable angina.**

d) **Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases) and eye diseases.**

Priapism: there have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) with the use of sildenafil. In the event of an erection that lasts more 4 hours, the patient should seek immediate medical attention. If not treated immediately, priapism may lead to penile tissue damage and permanent loss of potency.

SEGUREX® does not protect against sexually transmitted diseases, including the Human immunodeficiency Virus (HIV).

PRECAUTIONS

Before prescribing SEGUREX®, physicians should perform a complete medical assessment of the patient and determine the cause of the erectile dysfunction.

SEGUREX® should be used with caution in patients with anatomical deformation of the penis (such as angulation and cavernosal fibrosis or Peyronie's disease), and in patients with a predisposition to priapism or with conditions (such as sickle cell anemia, multiple myeloma or leukemia) that may predispose them to priapism. Although sildenafil has no effect on bleeding time when taken alone or with aspirin, in vitro studies show that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside, a nitric oxide donor. SEGUREX® should be used with caution in patients with risk factors for hemorrhage or active peptic ulceration. Given that sexual activity may increase the cardiac risk of some cardiovascular diseases, the cardiovascular status of the patient should be assessed prior to treatment with sildenafil.

Sildenafil should also be used with caution in patients with retinitis pigmentosa, since some of these patients have genetic disorders of retinal phosphodiesterases.

The efficacy and safety of sildenafil in association with other treatments for erectile dysfunction have not been studied. Therefore, such combination is not recommended until adequate research is conducted.

Drug interactions

Inhibitors of CYP3A4 and CYP2C9 isoenzymes may reduce sildenafil clearance.

Sildenafil is a weak inhibitor of CYP1A2, CYP2E9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 isoenzymes, so it is unlikely to alter the clearance of their substrates.

When coadministered with sildenafil to healthy volunteers, cimetidine caused a 56% increase in plasma sildenafil concentrations.

When sildenafil was administered with erythromycin, a specific CYP3A4 inhibitor, at steady state (500 mg bid for 5 days), there was a 182% increase in the area under the curve (AUC) of sildenafil. **Data from patients in clinical trials indicated a reduction In sildenafil clearance when coadministered with ketoconazol or itraconazole.**

In these patients, the starting dose should be the hall of the recommended dose.

On the other hand, concomitant administration of CYP3A4 inducers such as rifampicin may decrease plasma levels of sildenafil.

Single doses of antacid containing magnesium hydroxide/aluminum hydroxide do not affect the bioavailability of sildenafil.

CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers have no effect on sildenafil pharmacokinetics.

The area under the curve (AUC) of the active metabolite, N-desmethyl sildenafil, is increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. However, these effects on the active metabolite of sildenafil are not expected to be clinically relevant.

No significant interactions have been shown with tolbutamide or warfarin.

At the recommended dose, sildenafil does not potentiate the increase in bleeding time caused by aspirine (150 mg) or the hypotensive effect of alcohol in healthy volunteers.

A mean additional reduction In blood pressure was reported when sildenafil (100 mg) was coadministered with amlodipine (5 mg or 10 mg) to hypertensive patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to two different species of rodents.

Sildenafil was neither mutagenic in in vitro bacterial and Chinese hamster ovary cell assays, nor clastogenic in in vitro tests on human lymphocytes or in *in vivo* rat micronucleus assays.

There was no impairment of fertility in male or female rats given sildenafil.

No morphological or functional abnormalities in sperm were detected alter single 100 mg oral doses of sildenafil in healthy volunteers.

Pregnancy

Sildenafil should not be administered during pregnancy. There are no adequate and well-controlled studies of sildenafil in pregnant women.

No evidence of teratogenicity, embriotoxicity or fetotoxicity was observed in rats or rabbits that received sildenafil doses about 20 to 40 times greater than the maximum recommended human dose on a mg/m2 basis.

Nursing Mothers

It is not known whether sildenafil is excreted in human breast milk.

Pediatric Use

SEGUREX® is not indicated for use in children.

Geriatric use

Dose selection for patients aged > 65 years should be cautious. (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Reported adverse events are listed below according to incidence and body system involved. Those observed in >2% of patients are described as frequent; of these events, the ones more common on sildenafil than on placebo have been underlined. Adverse events seen in <2% of patients and with uncertain causal relationship to sildenafil are described as infrequent.

Body as a whole. *Frequent:* flu syndrome. *Infrequent:* lace edema, thirst, photosensitivity reaction, shock, asthenia, chills, accidental fall, accidental injury.

Cardiovascular. *Infrequent:* angina pectoris, AV block, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cardiac arrest, heart failure, abnormal electrocardiogram, syncope, cardiomyopathy.

Digestive. *Frequent:* dyspepsia diarrhea. Dyspepsia was more common at 100 mg than at lower doses. *Infrequent:* abdominal pain, vomiting, glossitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, rectal hemorrhage, gingivitis.

Metabolic and nutritional. *Infrequent:* gout, diabetes, peripheral edema, hyperglycemia, hypoglycemia, hypernatremia, hyperuricemia.

Hemic and Lymphatic. *Infrequent:* anemia, leukopenia.

Musculoskeletal. *Frequent:* back pain, arthralgia. Infrequent: arthritis, arthrosis, myalgia, tenosynovitis, myasthenia, bone pain, tendon rupture.

Neurological and Psychiatric. *Frequent:* headache dizziness. Infrequent: migraine, ataxia, hypertonia, neuropathy, tremor, vertigo, decreased reflexes, paresthesia, hypesthesia, mydriasis, tinnitus, depression, insomnia, nightmares, somnolence.

Respiratory. *Frequent:* respiratory tract infection, nasal congestion. Infrequent: asthma, dyspnea, pharyngitis, laryngitis, sinusitis, bronchitis, cough, increased sputum.

Skin and appendages. Frequent: flushing rash. Infrequent: herpes simplex, urticaria, pruritus, skin ulcer, contact dermatitis, exfoliative dermatitis, increased sweating.

Urogenital. *Frequent:* urinary tract infection. Infrequent: cystitis, nocturnal, abnormal ejaculation, genital edema, analgesia, urinary incontinence, breast enlargement.

No cases of priaprism were reported in the clinical studies.

Special senses. *Frequent:* abnormal vision (photophobia, blurred vision and changes in color vision). Abnormal vision was more common at 100 mg than at lower doses. Infrequent: conjunctivitis, photophobia, eye pain, dry eyes, cataract, eye hemorrhage, deafness, ear pain.

Laboratory. *Infrequent:* abnormal liver function tests.

OVERDOSAGE

Al doses up to 800 mg, the incidence rates of adverse events were higher than those seen at the usual recommended doses.

In case of overdose, go to the nearest Hospital

Alter carefully examining the patient and considering the amount of sildenafil ingested, the time interval since the ingestion and the potential contraindications of certain procedures, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate sildenafil clearance.

HOW SUPPLIED

Each package contains 4 film-coated tablets.

RECOMMENDED STORAGE

Store at room temperature, excursions permitted to 15-30 °C.

"This is a prescription medicine that must be used only under a doctor's care. Patients should not take this medicine again unless recommended and prescribed by a doctor."

"KEEP OUT OF THE REACH OF CHILDREN"