PROPOSED PACKAGE INSERT FOR SILREXIA 25 / 50 / 100

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Silrexia 25 film coated tablets

Silrexia 50 film coated tablets

Silrexia 100 film coated tablets

COMPOSITION

Active ingredient:

Silrexia 25: Each film coated tablet contains sildenafil citrate equivalent to 25 mg sildenafil.

Silrexia 50: Each film coated tablet contains sildenafil citrate equivalent to 50 mg sildenafil.

Silrexia 100: Each film coated tablet contains sildenafil citrate equivalent to 100 mg sildenafil.

Inactive ingredients:

Anhydrous calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and Opadry White (containing hypromellose, lactose monohydrate, titanium dioxide and triacetin).

Contains sugar: lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION

A 7.1.5 Vasodilators - peripheral

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Sildenafil increases blood flow to the penis, in response to sexual stimulation and thereby restores impaired erectile function.

Sildenafil is a selective phosphodiesterase type 5 (PDE5) inhibitor, an enzyme responsible for degrading cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. Sildenafil facilitates the effect of nitric oxide (NO) on the corpus cavernosum tissue during sexual stimulation resulting in increased cGMP levels, causing the smooth muscle to relax and blood to flow into the corpus cavernosum producing an erection. Without sexual stimulation, sildenafil has no effect on erections.

Pharmacokinetic properties:

Absorption:

Sildenafil is well absorbed after an oral dose with a mean absolute bioavailability of about 40 %. Peak plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. The oral pharmacokinetics of sildenafil is proportional over the recommended dose range (25 - 100 mg).

A high fat meal reduces absorption of sildenafil as shown by a reduction in the maximum plasma concentration (C_{max}) by 29 % and a mean delay in the time to peak concentration (T_{max}) of 60 minutes.

Distribution:

The mean steady state volume of distribution (Vss) for sildenafil is 105 liters. Sildenafil and its major circulating *N*-desmethyl metabolite exhibit a very high percentage (96 %) plasma protein binding, independent of total medicine concentrations.

Less than 0,0002 % of sildenafil remained in the semen of healthy volunteers at 90 minutes after dosing.

Metabolism:

Hepatic metabolism of sildenafil is predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) microsomal isoenzymes. Sildenafil is converted by *N*-demethylation to an active metabolite with a PDE selectivity profile similar to sildenafil. The terminal half-life of the *N*-desmethyl metabolite is approximately 4 hours.

Elimination:

Sildenafil is excreted as metabolites mainly in the faeces (approximately 80 % of administered oral dose) and to a lesser extent in the urine (approximately 13 % of administered oral dose).

Pharmacokinetics in special patient groups:

Elderly:

Healthy elderly volunteers, 65 years or over, cleared sildenafil less effectively from the plasma than did normal healthy volunteers, 18 to 45 years of age, as shown by a 40 % increase of AUC in older adults.

Renal insufficiency:

Sildenafil clearance was reduced in volunteers with severe renal impairment, with creatinine clearance values of Clcr ≤ 30 ml/min, resulting in increases in AUC (100 %) and C_{max} (88 %) compared to age-matched volunteers with no renal impairment (see **DOSAGE AND DIRECTIONS FOR USE**). The pharmacokinetics of a single dose of sildenafil (50 mg) were not altered in persons with mild (Clcr = 50 - 80 ml/min) to moderate (Clcr = 30 - 49 ml/min) renal impairment.

Hepatic insufficiency:

Sildenafil clearance was reduced in volunteers with hepatic cirrhosis (Child-Pugh A and B), resulting in increases in AUC by 84 % and C_{max} by 47 % compared to age-matched volunteers with no hepatic impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

INDICATIONS

Silrexia is indicated only for the treatment of erectile dysfunction.

SILREXIA IS NOT AN APHRODISIAC.

CONTRAINDICATIONS

Use of Silrexia is contraindicated in patients with a known hypersensitivity to sildenafil or any of the other components of Silrexia.

Consistent with its known effects on the nitric oxide/cGMP pathway (see PHARMACOLOGICAL ACTION), Silrexia was shown to potentiate the hypotensive effects of acute and chronic nitrates, and its co-administration with nitric oxide donors or nitrates in any form, either regularly or intermittently, is therefore contraindicated. Doctors should discuss the contraindication of Silrexia with concurrent organic nitrates.

- Severe hepatic impairment (e.g. cirrhosis).
- Severe renal impairment (e.g. creatinine clearance < 30 ml/min).
- Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ritonavir, saquinavir, ketoconazole, itraconazole) (see INTERACTIONS).
- Silrexia is contraindicated in patients who have loss of vision in one eye because of non-arteritic ischaemic optic neuropathy (NAION) regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure.

WARNINGS AND SPECIAL PRECAUTIONS

There is a potential cardiac risk with sexual activity in patients with pre-existing cardiovascular disease. Therefore, treatments for erectile dysfunction, including Silrexia, should generally not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

- A thorough medical history and physical examination should be undertaken to diagnose erectile dysfunction, determine potential underlying causes, and identify appropriate treatment.
- **Silrexia** has systemic vasodilatory properties that resulted in transient decrease in supine blood pressure in healthy volunteers. Medical practitioners should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.
- Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (such as aortic stenosis or hypertrophic obstructive cardiomyopathy), or those with the syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure.
- Concomitant administration of **Silrexia** to patients taking alpha-blocker therapy may lead to symptomatic hypotension in susceptible individuals (see **INTERACTIONS**). In order to minimise the potential for developing postural hypotension, patients should be haemodynamically stable on alpha-blocker therapy prior to initiating **Silrexia** treatment. Doctors should advise patients what to do in the event of postural hypotensive symptoms.
- **Silrexia** if prescribed, should be done with caution in the following patients:
    - Patients who have suffered a myocardial infarction, stroke or life-threatening dysrhythmia within the last 6 months.
    - Patients with resting hypotension (BP < 90/50) or hypertension (BP > 170/110).
    - Patients with cardiac failure or coronary artery disease causing unstable angina.

  - Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

- Patients should seek immediate medical assistance in the event of an erection that persists longer than 4 hours. Priapism (painful erections lasting longer than 6 hours) should be treated immediately, as penile tissue damage and permanent loss of potency could result.
- **Silrexia** 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).
- Combinations of **Silrexia** with other treatments for erectile dysfunction is not recommended as the safety and efficacy of such combinations have not been studied.
- **Silrexia** should be administered with caution to patients with bleeding disorders or active peptic ulceration.
- **Silrexia** has no effect on bleeding time, including during co-administration with aspirin.
- A sudden or bilateral decrease or loss of hearing (sensorineural deafness), with or without associated vestibular symptoms, has been reported with the use of PDE5 inhibitors, including **Silrexia**. There is insufficient information regarding the reversibility of the hearing loss and the role of underlying risk factors for hearing loss in individual subjects.
- Non arteritic anterior ischaemic optic neuropathy (NAION) with some loss of vision or irreversible blindness has been reported with the use of selective phosphodiesterase type-5 inhibitors including sildenafil (contained in **Silrexia**). NAION appears to be a class effect of these medicines. Most of these patients had risk factors such as low cup to disc ratio ("crowded disk"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidaemia and smoking. **Silrexia** should not be given to these patients.

Information for patients:

The use of **Silrexia** offers no protection against sexually transmitted diseases. Counseling of patients about protective measures necessary to guard against sexually transmitted diseases, including the human immunodeficiency virus (HIV/AIDS), should be considered. Precautions against unwanted pregnancy should be taken.

Effects on ability to drive and use machines:

Silrexia can lead to dizziness and altered vision and patients should be aware how they react to **Silrexia** and exercise caution before driving a vehicle, operating hazardous machinery or performing hazardous tasks.

Lactose monohydrate:

Silrexia contains lactose monohydrate (see **COMPOSITION**). Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take **Silrexia**.

INTERACTIONS

Effects of other medicines on Silrexia:

In vivo studies:

A 100 mg single dose of **Silrexia** co-administered with erythromycin 500 mg twice daily, resulted in a 182 % increase in sildenafil systemic exposure (AUC) at steady state. However with co-administration of sildenafil with azithromycin (500 mg daily for three days), no evidence was found of an effect on the AUC or other kinetic parameters of sildenafil.

Co-administration of a 100 mg single dose of **Silrexia** with saquinavir (1 200 mg three times daily) or ritonavir (500 mg twice daily) resulted in respectively a 210 % and 1 000 % increase in the AUC of sildenafil. (**Silrexia** had no effect on either the saquinavir or ritonavir pharmacokinetics.)

Inhibitors of cytochrome P450 (CYP) isoforms 3A4 and 2C9 isoenzymes that may reduce sildenafil clearance include the following:

Cimetidine, erythromycin, itraconazole, ketoconazole, HIV-protease inhibitors such as saquinavir. Ritonavir increases the plasma concentration of sildenafil significantly and such combinations should not be given unless absolutely essential.

No effect of concomitant medication on sildenafil pharmacokinetics acting as CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants), thiazide and related diuretics, loop and potassium sparing diuretics, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, beta-adrenoreceptor antagonists or inducers of CYP450 metabolism (such as rifampicin, barbiturates) have been noted.

Effects of Silrexia on other medicines:

Sildenafil may potentiate the hypotensive effect of acute and chronic nitrates. Therefore, the concomitant use of **Silrexia** and nitrates or nitric oxide donors is contraindicated (see **CONTRAINDICATIONS**).

Concomitant use of **Silrexia** and other antihypertensive medicines may potentiate the antihypertensive effect of these medicines. Symptomatic postural hypotension has been reported in patients who receive concomitant therapy with doxazosin and **Silrexia**. This includes reports of dizziness and light-headedness, but not syncope.

Silrexia did not potentiate the increase in bleeding time caused by aspirin. No significant interactions were shown between **Silrexia** and tolbutamide (250 mg) or warfarin (40 mg), both being metabolised by CYP2C9 isoenzyme.

Symptomatic hypotension may occur when **Silrexia** is administered concomitantly with alpha-blockers (see **WARNINGS AND SPECIAL PRECAUTIONS**).

PREGNANCY AND LACTATION

Silrexia is not indicated for use in women.

Silrexia was not found to be carcinogenic, teratogenic, embryotoxic or foetotoxic in animal studies.

Single 100 mg oral doses of sildenafil did not impair sperm motility or morphology.

DOSAGE AND DIRECTIONS FOR USE

Adults:

The recommended oral dose is 50 mg, taken as needed once a day, approximately one hour before sexual intercourse. The dose may be increased to 100 mg or decreased to 25 mg, depending on the efficacy and tolerance. The maximum recommended dose is 100 mg. The maximum recommended dosing frequency is once a day.

Use in patients with mild to moderately impaired renal function:

A starting dose of 25 mg should not be exceeded.

Use in patients with mild to moderately impaired hepatic function:

Since **Silrexia** clearance is reduced in patients with hepatic impairment, a starting dose of 25 mg should not be exceeded.

Use in elderly patients:

Healthy elderly volunteers (65 years or older) have a reduced clearance of **Silrexia**. A starting dose of 25 mg should be considered in patients older than 65 years of age.

Children

Silrexia is not indicated for use in children.

SIDE EFFECTS

Infections and infestations:

Less frequent: Infection, herpes simplex, cellulitis

Blood and the lymphatic system disorders:

Less frequent: Anaemia and leukopenia

Immune system disorders:

Less frequent: Allergic reaction, hypersensitivity reaction

Metabolism and nutrition disorders:

Less frequent: Thirst, gout, unstable diabetes, hyperglycaemia, hyperuricaemia, hypoglycaemic reaction and hypernatraemia

Psychiatric disorders:

Frequent: Insomnia, anxiety

Less frequent: Depression, abnormal dreams, anorgasmia

Nervous system disorders:

Frequent: Headache, dizziness

Less frequent: Ataxia, hypertonia, neuralgia, neuropathy, paraesthesia, tremor, somnolence, decreased reflexes, hypoaesthesia, migraine, seizures

Eye disorders:

Frequent: Cyanopsia, eye irritation, eye pain, ocular redness, photophobia, chromatopsia (mild and transient, predominantly colour tinge to vision)

Less frequent: Abnormal vision (increased perception of light, blurred vision), bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular oedema, conjunctivitis, eye haemorrhage, cataract, dry eyes, non-arteritic anterior ischaemic optic neuropathy (NAION)

Frequency unknown: Diplopia, temporary vision loss/decreased vision

Ear and labyrinth disorders:

Frequent: Vertigo

Less frequent: Tinnitus, deafness, ear pain

Cardiac disorders:

Frequent: Palpitations

Less frequent: Serious cardiovascular events, myocardial infarction, sudden cardiac death, ventricular dysrhythmia, angina pectoris, AV block, tachycardia, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy

Vascular disorders:

Frequent: Epistaxis

Less frequent: Cerebrovascular haemorrhage, transient ischaemic attack, hypertension (see **WARNINGS AND SPECIAL PRECAUTIONS**), hypotension, postural hypotension, vasodilatation (flushing), shock

Respiratory, thoracic and mediastinal disorders:

Frequent: Nasal congestion, dyspnoea

Less frequent: Asthma, laryngitis, pharyngitis, sinusitis, bronchitis, increased sputum, increased cough, respiratory disorder, respiratory tract infection

Gastrointestinal disorders:

Frequent: Dyspepsia, diarrhoea, nausea, vomiting

Less frequent: Abdominal pain, glossitis, colitis, dysphagia, gastritis, gastroenteritis, oesophagitis, stomatitis, dry mouth, rectal haemorrhage, gingivitis

Skin and subcutaneous tissue disorders:

Frequent: Flushing, erythema

Less frequent: Urticaria, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis, rash, photosensitivity reaction

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthritis, arthrosis, tendon rupture, tenosynovitis, myasthenia, synovitis, arthralgia, back pain, bone pain, myalgia

Renal and urinary disorders:

Less frequent: Cystitis, nocturia, urinary frequency, urinary incontinence, haematuria

Reproductive system and breast disorders:

Less frequent: Priapism (prolonged erection), breast enlargement, abnormal ejaculation, genital oedema, prostatic disorder

General disorders and administrative site conditions:

Frequent: Pyrexia (fever)

Less frequent: Face oedema, asthenia, pain, chills, accidental fall, chest pain, accidental injury, oedema, peripheral oedema, syncope

Investigations:

Less frequent: Abnormal liver function tests, abnormal electrocardiogram (ECG)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Supportive measures should be adopted as required, in the event of an overdose. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and not eliminated in the urine.

IDENTIFICATION

Silrexia 25: White, oval shaped, biconvex, film coated tablets, plain on one side and debossed with "B9" on the other side.

Silrexia 50: White, oval shaped, biconvex, film coated tablets, plain on one side and debossed with "C1" on the other side.

Silrexia 100: White, oval shaped, biconvex, film coated tablets, plain on one side and debossed with "436" on the other side.

PRESENTATION

Silrexia 25 is packed into silver aluminium foil/colourless transparent PVC film blister strips, in packs of 2 or 4 tablets per blister.

Silrexia 50 is packed into silver aluminium foil/colourless transparent PVC film blister strips, in packs of 2 or 4 tablets per blister.

Silrexia 100 is packed into silver aluminium foil/colourless transparent PVC film blister strips, in packs of 2 or 4 tablets per blister.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Protect from light.

Do not remove blister strips from outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Silrexia 25: 46/7.1.5/0100

Silrexia 50: 46/7.1.5/0101

Silrexia 100: 46/7.1.5/0102

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