PROFESSIONAL INFORMATION FOR TALVIOR 5

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

TALVIOR 5 film coated tablets.

COMPOSITION

Active ingredient:

Each tablet contains 5 mg tadalafil.

Inactive ingredients:

Colloidal silicone dioxide, croscarmellose sodium (Ac-Di-Sol), hydroxypropyl cellulose, magnesium stearate (Kosher Passover HyQual), Opadry Yellow (containing hypromellose, iron oxide yellow, macrogol, talc and titanium dioxide), povidone K-25 and sodium lauryl sulphate.

Contains sugar: Lactose monohydrate, 81,70 mg.

CATEGORY AND CLASS

A 7.1.5 Vasodilators – peripheral

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). In response to sexual stimulation, erectile dysfunction is improved by increasing blood flow to the penis.

When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by tadalafil produces increased levels of cGMP in the corpus cavernosum. An erection is produced as a result of smooth muscle relaxation and inflow of blood into the penile tissues. Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

Pharmacokinetic properties:

Absorption:

Tadalafil is readily absorbed after oral administration. Mean maximum plasma concentration (C_{max}) is achieved approximately 2 hours after dosing. Concomitant intake of food does not alter the absorption of tadalafil. No clinically significant effects on the rate and extent of absorption have been observed with relation to the time of dosing.

Distribution:

The mean volume of distribution of tadalafil is approximately 63 litres. At therapeutic concentrations, 94 % of tadalafil is bound to plasma proteins. Less than 0,0005 % of the administered dose is present in the semen of healthy subjects.

Metabolism:

Tadalafil is primarily metabolised to the major circulating metabolite methylcatechol glucuronide by the cytochrome P450 CYP3A4 isoenzyme. Methylcatechol glucuronide is approximately 13 000 fold less potent for PDE5 than tadalafil and is not expected to be clinically active at observed concentrations.

Elimination:

The mean half-life for tadalafil is 17,5 hours. The clearance of tadalafil is 0,59 mL/min/kg. Tadalafil is excreted predominantly as inactive metabolites. Approximately 61 % of the dose is excreted in the faeces and approximately 36 % of the dose is excreted in the urine.

Linearity:

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Exposure (AUC) increases proportionally over the dose range of 2,5 – 20 mg. Steady-state plasma concentrations are achieved within 5 days of once daily dosing.

Special populations:

Elderly patients:

Oral clearance of tadalafil is lower in healthy elderly subjects 65 years of age or older. The lower clearance rate results in a 25 % higher exposure (AUC) when compared to healthy subjects aged between 19 to 45 years. The effect of age is not clinically significant and does not warrant a dose adjustment.

Renal insufficiency:

The AUC of tadalafil is higher in patients with mild renal impairment (creatinine clearance 51 – 80 mL/min) or moderate renal impairment (creatinine clearance 31 – 50 mL/min) when compared to healthy patients. The AUC is higher in patients with renal insufficiency, including those on haemodialysis, when compared to healthy subjects.

Hepatic insufficiency:

The AUC of tadalafil in subjects with mild and moderate hepatic impairment (Child-Pugh class A and B) is comparable to the AUC in healthy patients, and no dosage adjustment is required. No data are available for the use of tadalafil in patients with severe hepatic impairment (Child-Pugh class C).

Patients with diabetes mellitus:

The AUC of tadalafil is approximately 19 % lower when compared to the AUC of healthy patients. The difference in exposure does not warrant a dose adjustment in patients with diabetes mellitus.

INDICATIONS

TALVIOR 5 is indicated for the treatment of erectile dysfunction. In order for TALVIOR 5 to be effective, sexual stimulation is required.

CONTRAINDICATIONS

- Hypersensitivity to tadalafil or any of the other ingredients of TALVIOR 5 (see **COMPOSITION**).
- Concomitant administration of TALVIOR 5 to patients who are using any form of organic nitrate (see **INTERACTIONS**).

- Patients with severe hepatic insufficiency (Child-Pugh class C).
- Previous experience of partial, sudden, temporary or permanent decrease or loss of vision in one or both eyes.
- Previous experience of unilateral or bilateral decrease or loss of hearing with or without associated vestibular symptoms.

WARNINGS AND SPECIAL PRECAUTIONS

An evaluation of erectile dysfunction should be made by determining the underlying cause and the identification of an appropriate course of treatment following appropriate medical assessment.

Cardiovascular disease:

TALVIOR 5 is not recommended for use in men with underlying cardiac conditions for whom sexual activity is not advised. Sexual activity carries a potential cardiac risk in patients with pre-existing cardiovascular disease.

TALVIOR 5 is not recommended for use in the following groups of patients with cardiovascular disease:

- Patients who experienced myocardial infarction within the last 90 days.
- Patients with unstable angina.
- Patients who experience angina during sexual intercourse.
- Patients with New York Heart Association class 2 or greater heart failure in the last 6 months.
- Patients with uncontrolled dysrhythmias.
- Patients with hypotension (< 90/50 mmHg).
- Patients with uncontrolled hypertension (> 170/100 mmHg).
- Patients who had a stroke within the last 6 months.

TALVIOR 5 has mild vasodilatory properties that may result in transient decreases in blood pressure. Patients with underlying cardiovascular disease could be adversely affected by such vasodilatory effects. Patients with conditions such as left ventricular outflow obstruction (aortic stenosis or idiopathic hypertrophic subaortic stenosis) may be sensitive to the vasodilatory effects of TALVIOR 5.

Non-arteritic anterior ischaemic optic neuropathy (NAION):

NAION has been reported with the use of PDE5 inhibitors, such as TALVIOR 5. NAION causes decreased vision, including permanent loss of vision.

It is not possible to determine whether NAION is directly related to the use of TALVIOR 5 or other factors. Caution is advised in patients older than 50 years of age, patients with coronary artery disease, diabetes, hyperlipidaemia, hypertension, low cup to disc ratio (crowded disc) or in patients who are known to smoke.

Treatment with TALVIOR 5 should be stopped and patients should seek immediate medical attention in the event of a sudden loss of vision.

Patients who have previously experienced NAION are at an increased risk of recurrence and may be adversely affected with the use of TALVIOR 5.

Impaired hearing:

Patients taking TALVIOR 5 may experience a sudden decrease or loss of hearing and must stop taking TALVIOR 5 and seek immediate medical attention. These events may be accompanied by tinnitus or dizziness. It is not possible to determine whether these events are directly related to the use of TALVIOR 5 or other factors.

Other treatment for erectile dysfunction:

The combination of TALVIOR 5 with other treatments for erectile dysfunction has not been studied and is not recommended (see **INTERACTIONS**).

Priapism:

Priapism has been associated with the use of TALVIOR 5. Patients who experience long-lasting erections for more than 4 hours, whether painful or not, should be instructed to seek immediate medical attention. Penile damage and permanent loss of potency may result if priapism is not treated immediately.

Patients with anatomical deformation of the penis, such as angulation, cavernosal fibrosis or Peyronie's disease, or patients with conditions such as sickle cell anaemia, multiple myeloma or leukaemia, are predisposed to priapism or painful erections and caution is advised.

Renal insufficiency:

TALVIOR 5 exposure (AUC) is increased in patients with severe renal impairment and clearance is not influenced by dialysis. Therefore TALVIOR 5 is not recommended in patients with severe renal impairment.

Hepatic insufficiency:

Safety and efficacy of once a day dosing with TALVIOR 5 have not been established in patients with hepatic insufficiency.

Bleeding disorders:

Caution is advised in patients with active peptic ulceration. **TALVIOR 5** has not been studied in patients with bleeding disorders.

Effects on ability to drive and use machinery:

TALVIOR 5 can cause side effects, such as dizziness or visual disturbances. Caution is advised before driving a vehicle or operating machinery, until the effects of TALVIOR 5 are known.

Lactose monohydrate:

TALVIOR 5 contains lactose monohydrate (see **COMPOSITION**). Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, lapp lactase deficiency or glucose-galactose malabsorption should not take TALVIOR 5.

INTERACTIONS

TALVIOR 5 does not significantly inhibit or induce CYP450 isoforms, including CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP2E1.

CYP3A4 inhibitors:

TALVIOR 5 is primarily metabolised by CYP3A4. Medicines such as ketoconazole, ritonavir or saquinavir, which are inhibitors of CYP3A4, can increase the exposure of tadalafil, as in TALVIOR 5. Caution is advised during concomitant treatment and the dose of **TALVIOR 5** should be limited to 10 mg not more than once every 24 hours. Other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole or grapefruit juice have not been studied, but may likely increase the exposure of TALVIOR 5 and caution is advised.

CYP3A4 inducers:

Medicines that induce CYP3A4 can decrease the exposure of tadalafil, as in TALVIOR 5. Rifampicin reduces tadalafil exposure by 88 % and C_{max} by 46 %. Other CYP inducers, such as carbamazepine, phenytoin or phenobarbitone may potentially decrease tadalafil exposure. No dose adjustment is warranted.

Antihypertensive medicine:

As a result of the vasodilatory properties of tadalafil, TALVIOR 5 may interfere with the blood pressure lowering effects of antihypertensive medicines. Caution is advised during concomitant treatment and appropriate clinical advice should be given to patients who are being treated with antihypertensive medicine and TALVIOR 5.

Alpha-adrenergic blockers:

Caution is advised with concomitant use of TALVIOR 5 and alpha-adrenergic medicine, due to the additive lowering effect of blood pressure, which may lead to symptomatic hypotension (such as fainting). Consideration should be given to ensure that the patient is stable on one medicine, prior to initiating the other at the lowest possible dose.

TALVIOR 5 has no clinically significant effect on the blood pressure lowering effects of tamsulosin.

The concomitant administration of doxazosin and **TALVIOR 5** may result in potentially clinical significant augmentation of the blood-lowering effects of doxazosin. Some patients may experience symptoms such as dizziness.

Nitrates:

The use of TALVIOR 5 in patients who are taking any form of organic nitrates (regularly or intermittently) is contraindicated (see **CONTRAINDICATIONS**). TALVIOR 5 potentiates the hypotensive effects of nitrates, due to the possible combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway.

At least 48 hours should elapse after the last dose of TALVIOR 5 before nitrate administration is considered.

Erectile dysfunction treatments:

The safety and efficacy of TALVIOR 5 in combination with other medicines used for erectile dysfunction have not been studied. The use of TALVIOR 5 in combination is not recommended.

Alcohol:

TALVIOR 5 does not affect alcohol plasma concentrations and alcohol does not affect the plasma concentrations of TALVIOR 5. Alcohol and TALVIOR 5 act as mild vasodilators. When taken in combination the blood pressure lowering effects of each individual compound may be increased. Substantial alcohol intake in combination with TALVIOR 5 can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness and headache.

Antacids:

The concomitant administration of TALVIOR 5 and antacids (magnesium hydroxide/aluminium hydroxide) reduces the apparent rate of absorption of TALVIOR 5 without altering exposure to TALVIOR 5.

H_2-antagonists:

The increase in gastric pH resulting from nizatidine does not cause a clinically significant effect on TALVIOR 5 pharmacokinetics.

Warfarin:

TALVIOR 5 does not cause a significant effect on the exposure of warfarin, nor does TALVIOR 5 affect changes in prothrombin time induced by warfarin.

Aspirin:

TALVIOR 5 does not potentiate the increase in bleeding time caused by aspirin.

Theophylline:

TALVIOR 5 does not cause a clinically significant effect on the pharmacokinetic or pharmacodynamic properties of theophylline.

Riociguat:

When PDE5 inhibitors are combined with riociguat, an additive systemic blood pressure lowering effect is seen. Riociguat augments the hypotensive effects of PDE5 inhibitors. Concomitant use of riociguat with PDE5 inhibitors, including TALVIOR 5, is not recommended.

Ethinylestradiol and terbutaline:

TALVIOR 5 increases the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this is uncertain.

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established.

TALVIOR 5 is not indicated for use in female patients.

DOSAGE AND DIRECTIONS FOR USE

For oral use.

Adult men:

The recommended dose is 5 mg taken once a day at approximately the same time of the day.

Men with renal impairment:

Dosage adjustments are not required in patients with mild to moderate renal impairment. Once a day dosing is not recommended in patients with severe renal impairment.

SIDE EFFECTS

Infections and infestations:

Less frequent: Bronchitis, cellulitis.

Blood and the lymphatic system disorders:

Less frequent: Anaemia, leukopenia.

Immune system disorders:

Less frequent: Hypersensitivity reactions, angioedema.

Psychiatric disorders:

Frequent: Insomnia, anxiety.

Less frequent: Somnolence.

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Hypaesthesia, paraesthesia, seizures, transient amnesia.

Eye disorders:

Frequent: Blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, eye pain.

Less frequent: Conjunctivitis, increased lacrimation, swelling of the eyelids, non-arteritic anterior ischaemic optic neuropathy (NAION).

Frequency unknown: Retinal vein occlusion, visual field defect.

Ear and labyrinth disorders:

Frequent: Vertigo.

Less frequent: Sudden decreased hearing, sudden loss of hearing, tinnitus.

Cardiac disorders:

Less frequent: Angina pectoris, chest pain, myocardial infarction, palpitations, tachycardia, dysrhythmias, sudden cardiac death.

Vascular disorders:

Frequent: Flushing.

Less frequent: Hypertension, hypotension, postural hypotension, syncope, stroke.

Respiratory, thoracic and mediastinal disorders:

Frequent: Nasal congestion, epistaxis.

Less frequent: Dyspnoea, oesophagitis, pharyngitis, rhinitis, cough, sinusitis.

Gastrointestinal disorders:

Frequent: Dyspepsia, diarrhoea, vomiting.

Less frequent: Dry mouth, dysphagia, gastritis, gastro-oesophageal reflux, loose stools, nausea, upper abdominal pain.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, rash, sweating, erythema, alopecia.

Frequency unknown: Exfoliative dermatitis, Stevens-Johnson syndrome, urticaria.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Back pain, myalgia.

Less frequent: Arthralgia, neck pain, pain in limbs.

Renal and urinary disorders:

Less frequent: Urinary tract infection, urinary frequency, urinary incontinence, haematuria.

Reproductive system and breast disorders:

Less frequent: Priapism, spontaneous penile erection, prolonged erections, gynaecomastia, haematospermia.

General disorders and administration site conditions:

Frequent: Pyrexia.

Less frequent: Asthenia, fatigue, pain, facial oedema, fluid retention.

Post-marketing experience:

Migraine has been reported post-marketing.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

In the event of overdose, treatment should be symptomatic and supportive. Haemodialysis contributes negligibly to the elimination of tadalafil, as in TALVIOR 5.

IDENTIFICATION

Yellow to light yellow, round shaped, bevelled edge, film coated tablets debossed with “337” on one side and plain on the other side.

PRESENTATION

OPA/Alu/PVC/aluminium blister strips or clear PVC/Aclar/aluminium blister strips containing 8, 10, 28 or 30 tablets. The blister strips are packed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light and moisture.

Store in original packaging.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

50/7.1.5/0661

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Registration date: 31 March 2020

Publication date: February 2022