August, 2022

UNICURE PHARMACEUTICAL LTD.

SUMMARY OF PRODUCT CHARACTERISTICS

FOR

VELAFIL

TADALAFIL 20mg TABLETS

TABLE OF CONTENT

1. Name of the medicinal product

Tadalafil 20 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 20 mg tadalafil.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

Yellow, capsule shaped, film coated tablet, with inscription "T 20" on one side and plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for VELAFIL Tadalafil to be effective for the treatment of erectile dysfunction, sexual stimulation is required.

It is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1).

Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.

4.2 Posology and method of administration

Posology

Erectile dysfunction in adult Men

In general, the recommended dose is 10 mg taken prior to anticipated sexual activity and with or without food. In those patients in whom Tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity.

The maximum dose frequency is once per day.

VELAFIL Tadalafil 10 mg and 20 mg is intended for use prior to anticipated sexual activity and it is not recommended for continuous daily use.

In patients who anticipate a frequent use of VELAFIL Tadalafil (i.e., at least twice weekly) a once daily regimen with the lowest doses of Tadalafil tablets might be considered suitable, based on patient choiceand the physician's judgement.

In these patients, the recommended dose is 5 mg taken once a day at approximately the same time of day. The dose may be decreased to 2.5 mg once a day based on individual Tolerability.

The appropriateness of continued use of the daily regimen should be reassessed periodically.

Pulmonary arterial hypertension

Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH.

Posology

The recommended dose is 40 mg (2 x 20 mg) taken once daily with or without food.

Special Populations

Elderly patients

Dose adjustments are not required in elderly patients.

Renal Impairment

Adult men with erectile dysfunction: Dose adjustments are not required in patients with mild to moderate renal impairment. For patients with severe renal impairment, 10 mg is the maximum recommended dose for on-demand treatment.

Once-a-day dosing of VELAFIL Tadalafil is not recommended in patients with severe renal impairment.(See sections 4.4 and 5.2.)

Pulmonary arterial hypertension: In patients with mild to moderate renal impairment a starting dose of 20 mg once per day is recommended. The dose may be increased to 40 mg once per day, based on individual efficacy and tolerability. In patients with severe renal impairment the use of VELAFIL Tadalafil is not recommended. (see sections 4.4 and 5.2).

Hepatic Impairment

Adult men with erectile dysfunction: For the treatment of erectile dysfunction using on-demand VELAFIL Tadalafil the recommended dose of Tadalafil is 10 mg taken prior to anticipated sexual activity and with or without food. There is limited clinical data on the safety of Tadalafil in patients with severe hepatic impairment (Child-Pugh class C); if prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. There are no available data about the administration of doses higher than 10 mg of VELAFIL Tadalafil to patients with hepatic impairment.

Once-a-day dosing of VELAFIL Tadalafil for the treatment of erectile dysfunction has not been evaluated in patients with hepatic impairment; therefore if prescribed, a careful individual benefit/risk evaluation must be undertaken by the prescribing physician. (See sections 4.4 and 5.2.)

Pulmonary arterial hypertension: Due to limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), following single doses of 10 mg, a starting dose of 20 mg once per day may be considered. If VELAFIL Tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of VELAFIL Tadalafil is not recommended. (see sections 4.4 and 5.2).

Men with Diabetes

Adult men with erectile dysfunction: Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of VELAFIL Tadalafil in the paediatric population with regard to the treatmentof erectile dysfunction.

The safety and efficacy of VELAFIL Tadalafil in the paediatric population has not yet been established. Currently available data are described in section 5.1.

Method of administration

Tablets for oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In clinical studies, VELAFIL Tadalafil was shown to augment the hypotensive effects of nitrates. This isthought to result from the combined effects of nitrates and VELAFIL Tadalafil on the nitric oxide/cGMPpathway. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated (See section 4.5).

Tadalafil must not be used in men with cardiac disease for whom sexual activity is inadvisable. Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease.

The following groups of patients with cardiovascular disease were not included in clinical trials and the use of tadalafil is therefore contraindicated:

- patients with myocardial infarction within the last 90 days,

- patients with unstable angina or angina occurring during sexual intercourse,

- patients with New York Heart Association Class 2 or greater heart failure in the last 6 months,

- patients with uncontrolled arrhythmias, hypotension (< 90/50mmHg), or uncontrolled hypertension,

- patients with a stroke within the last 6 months.

Tadalafil is contraindicated in 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 (see section 4.4).

The co-administration of PDE5 inhibitors, including VELAFIL tadalafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

4.4 Special warnings and precautions for use

Before treatment with VELAFILTadalafil

A medical history and physical examination should be undertaken to diagnose erectile dysfunction and determine potential underlying causes, before pharmacological treatment is considered.

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients, since there is a degree of cardiac risk associated with sexual activity. VELAFIL Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1), and as such potentiates the hypotensive effect of nitrates (see section 4.3).

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following an appropriate medical assessment. It is not known if VELAFIL tadalafil is effective in patients who have undergone pelvic surgery or radical non-nerve-sparing prostatectomy.

Cardiovascular

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischaemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical trials. Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors. However, it is not possible to definitively determine whether these events are related directly to these risk factors, to VELAFILtadalafil, to sexual activity, or to a combination of these or other factors.

The following groups of patients with cardiovascular disease were not included in PAH clinical studies:

- Patients with clinically significant aortic and mitral valve disease

- Patients with pericardial constriction

- Patients with restrictive or congestive cardiomyopathy

- Patients with significant left ventricular dysfunction

- Patients with life-threatening arrhythmias

- Patients with symptomatic coronary artery disease

- Patients with uncontrolled hypertension.

Since there are no clinical data on the safety of VELAFIL tadalafil in these patients, the use of VELAFIL Tadalafil is not recommended.

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 VELAFIL Tadalafil to patients with veno-occlusive disease, administration of tadalafil to such patients is not recommended. Should signs of pulmonary oedema occur when VELAFIL tadalafil is administered, thepossibility of associated PVOD should be considered.

VELAFIL Tadalafil has systemic vasodilatory properties that may result in transient decreases in blood pressure. Physicians should carefully consider whether their patients with certain underlying conditions, such as severe left ventricular outflow obstruction, fluid depletion, autonomic hypotension or patients with resting hypotension, could be adversely affected by such vasodilatory effects.

In patients who are taking alpha1 blockers, concomitant administration of VELAFIL Tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). The combination of VELAFIL Tadalafiland doxazosin is not recommended.

Vision

Visual defects and cases of NAION have been reported in connection with the intake of VELAFIL Tadalafil and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to VELAFIL Tadalafil or other PDE5 inhibitors. As this may be relevant for all patients exposed to Tadalafil, the patient should be advised that in case of sudden visual defect, he should stop taking VELAFIL Tadalafil and consult a physician immediately (see section 4.3).

Decreased or sudden hearing loss

Cases of sudden hearing loss have been reported after the use of VELAFIL Tadalafil. Although other risk factors were present in some cases (such as age, diabetes, hypertension and previous hearing loss history) patients should be advised to stop taking VELAFIL Tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

Due to increased VELAFIL Tadalafil exposure (AUC), limited clinical experience and the lack of abilityto influence clearance by dialysis, once-a-day dosing of Tadalafil is not recommended in patients with severe renal impairment.

There is limited clinical data on the safety of single-dose administration of VELAFIL Tadalafil in patients with severe hepatic insufficiency (Child-Pugh class C). If Tadalafil is prescribed, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Priapism and anatomical deformation of the penis

Patients who experience erections lasting 4 hours or more should be instructed to seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

VELAFIL Tadalafil 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).

Use with CYP3A4 inducers or inhibitors

Caution should be exercised when prescribing VELAFIL Tadalafil to patients using potent CYP3A4 inhibitors (ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin), as increased tadalafil exposure (AUC) has been observed if the medicinal products are combined (see section 4.5).

VELAFIL Tadalafil and other treatments for erectile dysfunction

The safety and efficacy of combinations of VELAFIL Tadalafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. The patients should be informed not to take VELAFIL Tadalafil in such combinations.

Prostacyclin and its analogues

The efficacy and safety of VELAFIL Tadalafil co-administered with prostacyclin or its analogues has notbeen studied in controlled clinical studies. Therefore, caution is recommended in case of co-administration.

Bosentan

The efficacy of VELAFIL Tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

Lactose

VELAFIL Tadalafil contains lactose. Patients with rare hereditary problems of galactose intolerance, totallactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg VELAFIL Tadalafil, as indicated below. With regard to those interaction studies where only the 10 mg Tadalafil dose was used, clinically relevant interactions at higher doses cannot be completely ruled out.

Effects of other substances on Tadalafil

Cytochrome P450 inhibitors

VELAFIL Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased Tadalafil (10 mg) exposure (AUC) 2-fold and Cmax by 15 %, relative to the AUC and Cmax values for tadalafil alone. Ketoconazole (400 mg daily) increased VELAFIL Tadalafil (20 mg) exposure (AUC) 4-fold and Cmax by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased VELAFIL Tadalafil (20 mg) exposure (AUC) 2-fold with no change in Cmax. Ritonavir (500 mg or 600 mg twice daily) increased VELAFIL Tadalafil (20 mg) single-dose exposure (AUC) by 32 % and decreased Cmax by 30 %. Although specific interactions have not been studied, other protease inhibitors, such as saquinavir, and other CYP3A4 inhibitors, such as erythromycin, clarithromycin, itraconazole,

and grapefruit juice, should be co-administered with caution, as they would be expected to increase plasma concentrations of VELAFIL Tadalafil (see section 4.4).

Consequently, the incidence of the adverse reactions listed in section 4.8 might be increased.

Transporters

The role of transporters (for example, p-glycoprotein) in the disposition of VELAFIL Tadalafil is notknown. Therefore, there is the potential of drug interactions mediated by inhibition of transporters.

P-glycoprotein substrates (e.g. digoxin)

VELAFIL Tadalafil (40 mg once per day) had no clinically significant effect on the pharmacokinetics of digoxin.

Cytochrome P450 inducers

A CYP3A4 inducer, rifampicin reduced Tadalafil AUC by 88 %, relative to the AUC values for Tadalafil alone (10 mg). This reduced exposure can be anticipated to decrease the efficacy of Tadalafil; the magnitude of decreased efficacy is unknown. Other inducers of CYP3A4, such as phenobarbital, phenytoin, and carbamazepine, may also decrease plasma concentrations of VELAFIL Tadalafil.

Endothelin-1 receptor antagonists (e.g. bosentan)

Bosentan (125 mg twice daily), a substrate of CYP2C9 and CYP3A4 and a moderate inducer of CYP3A4, CYP2C9 and possibly CYP2C19, reduced VELAFIL Tadalafil (40 mg once per day) systemicexposure by 42 % and Cmax by 27 % following multiple dose co-administration. The efficacy of VELAFIL Tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (seesections 4.4 and 5.1). Tadalafil did not affect the exposure (AUC and Cmax) of bosentan or its metabolites.

The safety and efficacy of combinations of VELAFIL Tadalafil and other endothelin-1 receptorantagonists have not been studied.

Effects of tadalafil on other medicinal products

Nitrates

In clinical studies, VELAFIL Tadalafil (5 mg, 10 mg and 20 mg) was shown to augment the hypotensive effects of nitrates. Therefore, administration of Tadalafil to patients who are using any form of organic nitrate is contraindicated (see section 4.3). Based on the results of a clinical study in which 150 subjects received daily doses of VELAFIL Tadalafil 20 mg for 7 days and 0.4 mg sublingual nitroglycerin at various times, this interaction lasted for more than 24 hours and was no longer detectable when 48 hourshad elapsed after the last VELAFIL Tadalafil dose. Thus, in a patient prescribed any dose of Tadalafil (2.5 mg to 20 mg), where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of Tadalafil before nitrate administration is considered. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Anti-hypertensives (including calcium channel blockers)

The co-administration of doxazosin (4 mg and 8 mg daily) and VELAFIL Tadalafil (5 mg daily dose and 20 mg as a single dose) increases the blood pressure-lowering effect of this alpha-blocker in a significant manner. This effect lasts at least 12 hours and may be symptomatic, including syncope. Therefore, this combination is not recommended (see section 4.4).

In interaction studies performed in a limited number of healthy volunteers, these effects were not reported with alfuzosin or tamsulosin. However caution should be exercised when using

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Tadalafil in patients treated with any alpha-blockers, and notably in the elderly. Treatments should be initiated at minimal dosage and progressively adjusted.

In clinical pharmacology studies, the potential for VELAFIL Tadalafil to augment the hypotensive effectsof antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied, including calcium-channel blockers (amlodipine), angiotensin converting enzyme(ACE) inhibitors (enalapril), beta-adrenergic receptor blockers (metoprolol), thiazide diuretics (bendrofluazide), and angiotensin II receptor blockers (various types and doses, alone or in combination with thiazides, calcium-channel blockers, beta-blockers, and/or alpha-blockers). VELAFIL Tadalafil (10 mg, except for studies with angiotensin II receptor blockers and amlodipine in which a 20 mg dose was applied) had no clinically significant interaction with any of these classes. In another clinical pharmacology study,VELAFIL Tadalafil (20 mg) was studied in combination with up to 4 classes of antihypertensives. In subjects taking multiple antihypertensives, the ambulatory-blood-pressure changes appeared to relate to the degree of blood pressure control. In this regard, study subjects whose blood pressure was well controlled, the reduction was minimal and similar to that seen in healthy subjects. In study subjects whose blood pressure was not controlled, the reduction was greater, although this reduction was not associated with hypotensive symptoms in the majority of subjects. In patients receiving concomitant antihypertensive medicinal products, VELAFIL Tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of alpha-blockers -doxazosin see above) is, in general, minor and not likely to be clinically relevant. Analysis of Phase 3 clinical trial data showed no difference in adverse events in patients taking tadalafil with or without antihypertensive medicinal products. However, appropriate clinical advice should be given to patients regarding a possible decrease in blood pressure when they are treated with antihypertensive medicinal products.

Riociguat

Preclinical studies showed an 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 VELAFIL Tadalafil, iscontraindicated (see section 4.3).

5-alpha reductase inhibitors

In a clinical trial that compared VELAFIL Tadalafil 5 mg co-administered with finasteride 5 mg to placebo plus finasteride 5 mg in the relief of BPH symptoms, no new adverse reactions were identified. However, as a formal drug-drug interaction study evaluating the effects of VELAFIL Tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when VELAFIL Tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)

When VELAFIL Tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesteraseinhibitor) in a clinical pharmacology study, there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate. Although this effect is minor and was of no clinical significance in this study, it should be considered when co-administering these medicinal products.

Oral contraceptive pill

At steady-state, VELAFIL Tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by26 % and Cmax by 70 % relative to oral contraceptive administered with placebo. There was no statistically significant effect of Tadalafil on levonorgestrel which suggests the effect of ethinylestradiol is due to inhibition of gut sulphation by VELAFIL Tadalafil. The clinical relevance of this finding is uncertain.

Terbutaline

A similar increase in AUC and Cmax seen with ethinylestradiol may be expected with oral administration of terbutaline, probably due to inhibition of gut sulphation by VELAFIL Tadalafil. The clinical relevance of this finding is uncertain.

Alcohol

Alcohol concentrations (mean maximum blood concentration 0.08 %) were not affected by co-administration with VELAFIL Tadalafil (10 mg or 20 mg). In addition, no changes in VELAFIL Tadalafil concentrations were seen 3 hours after co-administration with alcohol. Alcohol was administered in a manner to maximise the rate of alcohol absorption (overnight fast with no food until 2 hours after alcohol).

VELAFIL Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7g/kg or approximately 180 mL of 40 % alcohol [vodka] in an 80 kg male) but, in some subjects, posturaldizziness and orthostatic hypotension were observed. When VELAFIL Tadalafil was administered with lower doses of alcohol (0.6 g/kg), hypotension was not observed and dizziness occurred with similar frequency to alcohol alone. The effect of alcohol on cognitive function was not augmented by VELAFIL Tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products

VELAFIL Tadalafil is not expected to cause clinically significant inhibition or induction of the clearanceof medicinal products metabolised by CYP450 isoforms. Studies have confirmed that VELAFIL Tadalafil does not inhibit or induce CYP450 isoforms, including CYP3A4, CYP1A2, CYP2D6, CYP2E1, CYP2C9 and CYP2C19.

CYP2C9 substrates (e.g. R-warfarin)

VELAFIL Tadalafil (10 mg and 20 mg) had no clinically significant effect on exposure (AUC) to S-warfarin or R-warfarin (CYP2C9 substrate), nor did Tadalafil affect changes in prothrombin time induced by warfarin.

Aspirin

VELAFIL Tadalafil (10 mg and 20 mg) did not potentiate the increase in bleeding time caused byacetylsalicylic acid.

Antidiabetic medicinal products

Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of VELAFIL Tadalafil in pregnant women. Animal studies do notindicate direct or indirect harmful effects with respect to pregnancy**,** embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable toavoid the use of VELAFIL Tadalafil during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of VELAFIL Tadalafilin milk. A risk to the suckling child cannot be excluded.VELAFIL Tadalafil should not be used during breast-feeding.

Fertility

Effects were seen in dogs that might indicate impairment of fertility. Two subsequent clinical studies suggest that this effect is unlikely in humans, although a decrease in sperm concentration was seen in some men (see sections 5.1 and 5.3).

4.7 Effects on ability to drive and use machines

VELAFIL Tadalafil has negligible influence on the ability to drive or use machines. Although the frequency of reports of dizziness in placebo and Tadalafil arms in clinical trials was similar, patients should be aware of how they react to VELAFIL Tadalafil, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile of VELAFIL **Tadalafil in erectile dysfunction**

The most commonly reported adverse reactions in patients taking VELAFIL Tadalafil for the treatment of erectile dysfunction or benign prostatic hyperplasia were headache, dyspepsia, back pain and myalgia, in which the incidences increase with increasing dose of VELAFIL Tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with VELAFIL Tadalafil once-a-day dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated summary of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 8022 patients on VELAFIL Tadalafil and 4422 patients on placebo) for on-demand and once-a-day treatment of erectile dysfunction and the once-a-day treatment of benign prostatic hyperplasia.

Frequency convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**
Immune system disorders			
		Hypersensitivity reactions	Angioedema2
Nervous system disorders			
	Headache	Dizziness	Stroke1 (including haemorrhagic events), Syncope, Transient ischaemic attacks1, Migraine2, Seizures2, Transient amnesia
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischaemic optic neuropathy (NAION)2, Retinal vascular occlusion2
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss

Cardiac disorders1			
		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris2, Ventricular arrhythmia2
Vascular disorders			
	Flushing	Hypotension3, Hypertension	
Respiratory, thoracic and mediastinal disorders			
	Nasal congestion	Dyspnoea, Epistaxis	
Gastrointestinal disorders			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux	
Skin and subcutaneous tissue disorders			
		Rash	Urticaria, Stevens-Johnson syndrome2, Exfoliative dermatitis2, Hyperhydrosis (sweating)
Musculoskeletal and connective tissue disorders			
	Back pain, Myalgia, Pain in extremity		
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
		Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
General disorders and administration site conditions			
		Chest pain1, Peripheral oedema, Fatigue	Facial oedema2, Sudden cardiac death1,2

1 Most of the patients had pre-existing cardiovascular risk factors (see section 4.4).

2 Postmarketing surveillance reported adverse reactions not observed in placebo-controlled clinical trials.

3 More commonly reported when Tadalafil is given to patients who are already taking antihypertensive medicinal products.

Description of selected adverse reactions

A slightly higher incidence of ECG abnormalities, primarily sinus bradycardia, has been reported in patients treated with VELAFIL Tadalafil once a day as compared with placebo. Most of these ECG abnormalities were not associated with adverse reactions.

Other special populations

Data in patients over 65 years of age receiving VELAFIL Tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with VELAFIL Tadalafil taken on demand for the treatment of erectile dysfunction, diarrhoea was reported more frequently in patients over 65 years of age. In clinical trials with VELAFIL Tadalafil 5

taken once a day for the treatment of benign prostatic hyperplasia, dizziness and diarrhoea were reported more frequently in patients over 75 years of age.

Summary of the safety profile of VELAFIL **Tadalafil in pulmonary arterial hypertension**

The most commonly reported adverse reactions, occurring in ≥ 10 % of patients in the VELAFIL Tadalafil 40 mg treatment arm were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharingitis and pain in extremity. The adverse reactions reported were transient, and generally mild or moderate. Adverse reaction data are limited in patients over 75 years of age.

In the pivotal placebo-controlled study of VELAFIL Tadalafil for the treatment of PAH, a total of 323 patients were treated with VELAFIL Tadalafil at doses ranging from 2.5 mg to 40 mg once daily and 82 patients were treated with placebo. The duration of treatment was 16 weeks. The overall frequency of discontinuation due to adverse events was low (tadalafil 11 %, placebo 16 %). Three hundred and fifty seven (357) patients who completed the pivotal study entered a long-term extension study. Doses studied were 20 mg and 40 mg once daily.

Tabulated summary of adverse reactions

The table below lists the adverse reactions reported during the placebo-controlled clinical study in patients with PAH treated with VELAFIL Tadalafil. Also included in the table are some adverse reactions which have been reported in clinical studies and/or post marketing with VELAFIL Tadalafil inthe treatment of male erectile dysfunction. These events have either been assigned a frequency of "Not known," as the frequency in PAH patients cannot be estimated from the available data or assigned a frequency based on the clinical study data from the pivotal placebo-controlled study of VELAFIL Tadalafil.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Very common (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Not known1**
Immune system disorders				
	Hypersensitivity reactions5			Angioedema
Nervous system disorders				
Headache6	Syncope, Migraine5	Seizures5, Transient amnesia5		Stroke2 (including haemorrhagic events)
Eye disorders				
	Blurred vision			Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
Ear and labyrinth disorders				
		Tinnitus		Sudden hearing loss
Cardiac disorders				

	Palpitations2, 5	Sudden cardiac death2, 5, Tachycardia2, 5	Unstable angina pectoris, Ventricular arrhythmia, Myocardial Infarction2
Vascular disorders			
Flushing	Hypotension	Hypertension	
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis (including nasal congestion, sinus congestion and rhinitis)	Epistaxis		
Gastrointestinal disorders			
Nausea, Dyspepsia (including abdominal pain/discomfort3)	Vomiting, Gastroesophageal reflux		
Skin and subcutaneous tissue disorders			
	Rash	Urticaria5, Hyperhydrosis (sweating)5	Stevens-Johnson Syndrome, Exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders			
Myalgia, Back pain Pain in extremity (including limb discomfort)			
Renal and urinary disorders			
		Haematuria	
Reproductive system and breast disorders			
	Increased uterine bleeding4	Priapism5, Penile haemorrhage, Haematospermia	Prolonged erections
General disorders and administration site conditions			
	Facial oedema, Chest pain2		

(1) Events not reported in registration studies and cannot be estimated from the available data. The adverse reactions have been included in the table as a result of postmarketing or clinical study data from the use of VELAFIL Tadalafil in the treatment of erectile dysfunction.

(2) Most of the patients in whom these events have been reported had pre-existing cardiovascular risk factors.

(3) Actual MedDRA terms included are abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and stomach discomfort.

(4) Clinical non-MedDRA term to include reports of abnormal/excessive menstrual bleeding conditions such as menorrhagia, metrorrhagia, menometrorrhagia, or vaginal hemorrhage.

(5) The adverse reactions have been included in the table as a result of postmarketing or clinical study data from the use of VELAFIL Tadalafil in the treatment of erectile dysfunction; and in addition, the frequency estimates are based on only 1 or 2 patients experiencing the adverse reaction in the pivotal placebocontrolled study of Tadalafil.

(6) Headache was the most commonly reported adverse reaction. Headache may occur at the beginning of therapy; and decreases over time even if treatment is continued.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses of up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses.

In cases of overdose, standard supportive measures should be adopted, as required. Haemodialysis contributes negligibly to VELAFIL Tadalafil elimination.

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5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs used in erectile dysfunction, ATC Code: G04BE08.

Mechanism of action

VELAFIL Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate(cGMP)-specific phosphodiesterase type 5 (PDE5).

Erectile dysfunction

When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by Tadalafil produces increased levels of cGMP in the corpus cavernosum. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. VELAFIL Tadalafil has no effect in the treatment of erectile dysfunction in the absence of sexual stimulation.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is associated with impaired release of Nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.

Pharmacodynamic effects

Studies *in vitro* have shown that VELAFIL Tadalafil is a selective inhibitor of PDE5. PDE5 is an enzymefound in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of VELAFIL Tadalafil is more potent on

PDE5 than

on other phosphodiesterases. VELAFIL Tadalafil is > 10,000-fold more potent for PDE5 than for PDE1, PDE2, and PDE4 enzymes which are found in the heart, brain, blood vessels, liver, and other organs. VELAFIL Tadalafil is > 10,000-fold more potent for PDE5 than for PDE3, an enzyme found in the heart and blood vessels.

This selectivity for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility. Additionally, Tadalafil is approximately 700-fold more potent for PDE5 than for PDE6, an enzyme which is found in the retina and is responsible for phototransduction. VELAFIL Tadalafil is also > 10,000-fold more potent for PDE5 than for PDE7 through PDE10.

Clinical efficacy and safety

Erectile dysfunction

Three clinical studies were conducted in 1,054 patients in an at-home setting to define the period of responsiveness. Tadalafil demonstrated statistically significant improvement in erectile function and the ability to have successful sexual intercourse up to 36 hours following dosing, as well as patients' ability to attain and maintain erections for successful intercourse compared to placebo as early as 16 minutes following dosing.

VELAFIL Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), etiologies, ages (range 21-86 years), and ethnicities. Most patients reported erectile dysfunction of at least 1 year in duration. In the primary efficacy studies of general populations, 81 % of patients reported that Tadalafil improved their erections as compared to 35 % with placebo. Also, patients with erectile dysfunction in all severity categories reported improved erections whilst taking Tadalafil (86 %, 83 %, and 72 % for mild, moderate, and severe, respectively, as compared to 45 %, 42 %, and 19 % with placebo). In the primary efficacy studies, 75 % of intercourse attempts were successful in Tadalafil treated patients as compared to 32 % with placebo.

In a 12-week study performed in 186 patients (142 Tadalafil, 44 placebo) with erectile dysfunction secondary to spinal cord injury, VELAFIL Tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with VELAFIL Tadalafil 10 mg or 20 mg (flexible-dose, on demand) of 48 % as compared to 17 % with placebo.

Efficacy in patients with pulmonary arterial hypertension (PAH)

A randomised, double-blind, placebo-controlled study was conducted in 405 patients with pulmonary arterial hypertension. Allowed background therapy included bosentan (stable maintenance dose up to 125 mg twice daily) and chronic anticoagulation, digoxin, diuretics and oxygen. More than half (53.3 %) of the patients in the study were receiving concomitant bosentan therapy.

Patients were randomised to one of five treatment groups (VELAFIL Tadalafil 2.5 mg, 10 mg, 20 mg, 40mg, or placebo). Patients were at least 12 years of age and had a diagnosis of PAH that was idiopathic, related to collagen disease, related to anorexigen use, related to human immunodeficiency virus (HIV) infection, associated with an atrial-septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt (for example, ventricular septal defect, patent ductus arteriosus). The mean age of all patients was 54 years (range 14 to 90 years) with the majority ofpatients being Caucasian (80.5 %) and female (78.3 %). Pulmonary arterial hypertension (PAH) etiologies were predominantly idiopathic PAH (61.0 %) and related to collagen vascular disease (23.5 %). The majority of patients had a World Health Organization (WHO) Functional Class III (65.2 %) or II (32.1 %). The mean baseline 6-minute-walk-distance (6MWD) was 343.6 meters.

The primary efficacy endpoint was the change from baseline at week 16 in 6-minute walk distance (6MWD). Only VELAFIL Tadalafil 40 mg achieved the protocol defined level of significance with a placebo adjusted median increase in 6MWD of 26 metres (p=0.0004; 95 % CI: 9.5, 44.0; Pre-specified

Hodges-Lehman method) (mean 33 metres, 95 % CI: 15.2, 50.3). The improvement in walk distance was apparent from 8 weeks of treatment. Significant improvement ($p<0.01$) in the 6MWD was demonstrated at week 12 when the patients were asked to delay taking study medicinal product in order to reflect trough active substance concentration. Results were generally consistent in subgroups according to age, gender, PAH aetiology and baseline WHO functional class and 6MWD. The placebo-adjusted median increase in 6MWD was 17 metres ($p=0.09$; 95 % CI: : -7.1, 43.0; Prespecified Hodges-Lehman method) (mean 23 metres, 95 % CI; -2.4, 47.8) in those patients who received VELAFIL Tadalafil 40 mg in addition to their concomitant bosentan (n=39), and was 39 metres ($p<0.01$,95 % CI:13.0, 66.0; Pre-specified Hodges-Lehman method) (mean 44 metres, 95 % CI: 19.7, 69.0) in those patients who received VELAFIL Tadalafil 40 mg alone (n=37).

The proportion of patients with improvement in WHO functional class by week 16 was similar in the VELAFIL Tadalafil 40 mg and placebo groups (23 % vs. 21 %). The incidence of clinical worsening by week 16 in patients treated with Tadalafil 40 mg (5 %; 4 of 79 patients) was less than placebo (16 %; 13 of 82 patients). Changes in the Borg dyspnoea score were small and non-significant with both placebo and VELAFIL Tadalafil 40 mg.

Paediatric population

A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. The randomised, double-blind, placebo-controlled, parallel, 3-arm study of VELAFIL Tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double-blind period where patients were randomised to Tadalafil 0.3 mg/kg, Tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the Tadalafil 0.3 mg/kg group ($p = 0.307$) and -59.1 m in the Tadalafil 0.6 mg/kg group ($p = 0.538$). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of VELAFIL Tadalafil and with adverse events (AEs) expectedin a paediatric DMD population receiving corticosteroids.

The European Medicines Agency has waived the obligation to submit the results of studies in all subsets of the paediatric population in the treatment of the erectile dysfunction and in one or more subsets of the paediatric population in the treatment of pulmonary arterial hypertension. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

VELAFIL Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (Cmax) is achieved at a median time of 2 hours after dosing. Absolute bioavailability of Tadalafil following oral dosing has not been determined.

The rate and extent of absorption of Tadalafil are not influenced by food, thus Tadalafil may be taken with or without food. The time of dosing (morning versus evening after a single 10 mg administration) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 liters, indicating that Tadalafil is distributed into tissues. At therapeutic concentrations, 94 % of Tadalafil in plasma is bound to proteins. Protein binding is not affected by impaired renal function.

Less than 0.0005 % of the administered dose appeared in the semen of healthy subjects.

Biotransformation

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. The major circulating metabolite is the methylcatechol glucuronide. This metabolite is at least 13,000-fold less potent than Tadalafil for PDE5. Consequently, it is not expected to be clinically active at observed metabolite concentrations.

Elimination

The mean oral clearance for VELAFIL Tadalafil is 2.5 L/h and the mean half-life is 17.5 hours in healthysubjects. Tadalafil is excreted predominantly as inactive metabolites, mainly in the faeces (approximately 61 % of the dose) and to a lesser extent in the urine (approximately 36 % of the dose).

Linearity/Non-Linearity

Over a dose range of 2.5 mg to 20 mg, exposure (AUC) increases proportionally with dose in healthy subjects. Between 20 mg to 40 mg, a less than proportional increase in exposure is observed.

During VELAFIL Tadalafil 20 mg and 40 mg once daily dosing, steady-state plasma concentrations are attained within 5 days, and exposure is approximately 1.5 fold of that after a single dose.

Population Pharmacokinetics

Pharmacokinetics determined with a population approach in patients with erectile dysfunction are similar to pharmacokinetics in subjects without erectile dysfunction.

In patients with pulmonary hypertension not receiving concomitant bosentan, the average VELAFIL Tadalafil exposure at steady-state following 40 mg was 26 % higher when compared to those of healthy volunteers. There were no clinically relevant differences in Cmax compared to healthy volunteers. The results suggest a lower clearance of VELAFIL Tadalafil in patients with pulmonary hypertension compared to healthy volunteers.

Special Populations

Elderly

Healthy elderly subjects (65 years or over) had a lower oral clearance of VELAFIL Tadalafil, resulting in25 % higher exposure (AUC) relative to healthy subjects aged 19 to 45 years. This effect of age is not clinically significant and does not warrant a dose adjustment.

Renal Insufficiency

In clinical pharmacology studies using single dose VELAFIL Tadalafil (5 mg to 20 mg), Tadalafil exposure (AUC) approximately doubled in subjects with mild (creatinine clearance 51 to 80 mL/min) or moderate (creatinine clearance 31 to 50 mL/min) renal impairment and in subjects with end-stage renal disease on dialysis. In haemodialysis patients, Cmax was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to VELAFIL Tadalafil elimination.

Due to increased VELAFIL Tadalafil exposure (AUC), limited clinical experience, and the lack of abilityto influence clearance by dialysis, Tadalafil is not recommended in patients with severe renal impairment.

Hepatic Insufficiency

Tadalafil exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh class A and B) is comparable to exposure in healthy subjects when a dose of 10 mg is administered. There is limited clinical data on the safety of VELAFIL Tadalafil in patients with severe hepatic insufficiency (Child-Pugh class C). There are no available data about the administration of once-a-day dosing of tadalafil to patients with hepatic impairment. If VELAFIL Tadalafil is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients with diabetes

VELAFIL Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects after a 10 mg dose. This difference in exposure does not warrant a dose adjustment.

Race

Pharmacokinetic studies have included subjects and patients from different ethnic groups, and no differences in the typical exposure to VELAFIL Tadalafil have been identified. No dose adjustment iswarranted.

Gender

In healthy female and male subjects following single and multiple-doses of VELAFIL Tadalafil, noclinically relevant differences in exposure were observed. No dose adjustment is warranted.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

There was no evidence of teratogenicity, embryotoxicity, or foetotoxicity in rats or mice that received up to 1000 mg/kg/day Tadalafil. In a rat prenatal and postnatal development study, the no observed effect dose was 30 mg/kg/day. In the pregnant rat the AUC for calculated free drug at this dose was approximately 18-times the human AUC at a 20 mg dose.

There was no impairment of fertility in male and female rats. In dogs given VELAFIL Tadalafil daily for 6 to 12 months at doses of 25 mg/kg/day (resulting in at least a 3-fold greater exposure [range 3.7-18.6] than seen in humans given a single 20 mg dose) and above, there was regression of the seminiferous tubular epithelium that resulted in a decrease in spermatogenesis in some dogs. See also section 5.1.

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6. Pharmaceutical particulars

6.1 List of excipients

Sodium dodecyl sulfate

lactose

3% Hypromellose

Sodium Carboxymethyl Starch

microcrystalline cellulose Starch

95% alcohol

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
The film-coated tablets are packed in PVC/PE/PVdC clear Aluminum blisters.

Pack sizes: 10*1*6 or 60 tablets

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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7. Marketing authorisation holder

Unicure Pharnaceutical Limited

Lagos- Benin Express way

Ikofa

Ijebu- Ode