SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

Ultralinc 5 mg caplet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each caplet contains 5 mg tadalafil.

{For a full list of excipients,see section 6.1}

3. PHARMACEUTICAL FORM:

Caplet.
Brown caplet with a broken line on one side and plain on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Treatment of erectile dysfunction in adult males.

In order for 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

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.

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

Pulmonary arterial hypertension

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

The recommended dose is 40 mg taken once daily with or without food.

Method of administration

Caplets 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, tadalafil was shown to augment the hypotensive effects of nitrates. This is thought to result from the combined effects of nitrates and tadalafil on the nitric oxide/cGMP pathway. 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 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 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 Tadalafil

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. Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure, and as such potentiates the hypotensive effect of nitrates.

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 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 tadalafil, to sexual activity, or to a combination of these or other factors.

Since there are no clinical data on the safety of tadalafil in these patients, the use of 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 tadalafil to patients with veno-occlusive disease, administration of tadalafil to such patients is not recommended. Should signs of pulmonary oedema occur when tadalafil is administered, the possibility of associated PVOD should be considered.

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 alpha$_1$ blockers, concomitant administration of tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Analyses of observational data suggest an increased risk of acute NAION in men with erectile dysfunction following exposure to 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 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 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 tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing.

Renal and hepatic impairment

Due to increased tadalafil exposure (AUC), limited clinical experience and the lack of ability to 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 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.

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 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

Tadalafil and other treatments for erectile dysfunction

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

Prostacyclin and its analogues

The efficacy and safety of tadalafil co-administered with prostacyclin or its analogues has not been studied in controlled clinical studies. Therefore, caution is recommended in case of co-administration.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were conducted with 10 mg and/or 20 mg 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

Tadalafil is principally metabolised by CYP3A4. A selective inhibitor of CYP3A4, ketoconazole (200 mg daily), increased tadalafil (10 mg) exposure (AUC) 2-fold and C_{max} by 15 %, relative to the AUC and C_{max} values for tadalafil alone. Ketoconazole (400 mg daily) increased tadalafil (20 mg) exposure (AUC) 4-fold and C_{max} by 22 %. Ritonavir, a protease inhibitor (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) exposure (AUC) 2-fold with no change in C_{max}. Ritonavir (500 mg or 600 mg twice daily) increased 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 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 tadalafil is not known. Therefore, there is the potential of drug interactions mediated by inhibition of transporters.

P-glycoprotein substrates (e.g. digoxin)

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 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 tadalafil (40 mg once per day) systemic exposure by 42 % and Cmax by 27 % following multiple dose co-administration. The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 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 tadalafil and other endothelin-1 receptor antagonists have not been studied.

Effects of tadalafil on other medicinal products

Nitrates

In clinical studies, 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 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 hours had elapsed after the last 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 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 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 tadalafil to augment the hypotensive effects of 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). 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, 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, 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 tadalafil, is contraindicated (see section 4.3).

5-alpha reductase inhibitors

In a clinical trial that compared 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 tadalafil and 5-alpha reductase inhibitors (5-ARIs) has not been performed, caution should be exercised when tadalafil is co-administered with 5-ARIs.

CYP1A2 substrates (e.g. theophylline)

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) 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, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26 % 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 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 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 tadalafil (10 mg or 20 mg). In addition, no changes in 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).

Tadalafil (20 mg) did not augment the mean blood pressure decrease produced by alcohol (0.7 g/kg or approximately 180 mL of 40 % alcohol [vodka] in an 80 kg male) but, in some subjects, postural dizziness and orthostatic hypotension were observed. When 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 tadalafil (10 mg).

Cytochrome P450 metabolised medicinal products

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

CYP2C9 substrates (e.g. R-warfarin)

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

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

Antidiabetic medicinal products

Specific interaction studies with antidiabetic medicinal products were not conducted.

4.6 Pregnancy and Lactation

Pregnancy

There are limited data from the use of tadalafil in pregnant women. Animal studies do not indicate 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 to avoid the use of Tadalafil during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. 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

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 Tadalafil, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile of tadalafil in erectile dysfunction

The most commonly reported adverse reactions in patients taking 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 tadalafil. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with 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 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	Angioedema[2]
Nervous system disorders			
	Headache	Dizziness	Stroke[1] (including haem events), Syncope, Trans ischaemic attacks[1], Migr Seizures[2], Transient am
Eye disorders			
		Blurred vision, Sensations described as eye pain	Visual field defect, Swel eyelids, Conjunctival hy Non-arteritic anterior isc optic neuropathy (NAIO vascular occlusion[2]
Ear and labyrinth disorders			
		Tinnitus	Sudden hearing loss
Cardiac disorders[1]			
		Tachycardia, Palpitations	Myocardial infarction, U angina pectoris[2], Ventric arrhythmia[2]
Vascular disorders			
	Flushing	Hypotension[3], 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-Johns syndrome[2], Exfoliative d Hyperhydrosis (sweatin
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 haemo Haematospermia
General disorders and administration site conditions			
		Chest pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudder death[1,2]

[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 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 tadalafil in clinical trials, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical trials with 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 tadalafil 5 mg 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 Tadalafil in pulmonary arterial hypertension

The most commonly reported adverse reactions, occurring in ≥ 10 % of patients in the 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 tadalafil for the treatment of PAH, a total of 323 patients were treated with 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 tadalafil. Also included in the table are some adverse reactions which have been reported in clinical studies and/or post marketing with tadalafil in the 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 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 kno**
Immune system disorders				
	Hypersensitivity reactions[5]			Angioed
Nervous system disorders				
Headache[6]	Syncope, Migraine[5]	Seizures[5], Transient amnesia[5]		Stroke[2] haemorr events)
Eye disorders				
	Blurred vision			Non-arte anterior optic ne (NAION vascular Visual fi
Ear and labyrinth disorders				
		Tinnitus		Sudden loss
Cardiac disorders				
	Palpitations[2, 5]	Sudden cardiac death[2, 5], Tachycardia[2, 5]		Unstable pectoris arrhythn Myocard Infarctio
Vascular disorders				
Flushing	Hypotension	Hypertension		
Respiratory, thoracic and mediastinal disorders				
Nasopharyngitis (including nasal congestion, sinus congestion and	Epistaxis			

rhinitis)				
Gastrointestinal disorders				
Nausea, Dyspepsia (including abdominal pain/discomfort[3])	Vomiting, Gastroesophageal reflux			
Skin and subcutaneous tissue disorders				
	Rash	Urticaria[5], Hyperhydrosis (sweating)[5]		Stevens Syndron Exfoliati dermatit
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 bleeding[4]	Priapism[5], Penile haemorrhage, Haematospermia		Prolong
General disorders and administration site conditions				
	Facial oedema, Chest pain[2]			

(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 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 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.

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 tadalafil elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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. 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 tadalafil is a selective inhibitor of PDE5. PDE5 is an enzyme found in corpus cavernosum smooth muscle, vascular and visceral smooth muscle, skeletal muscle, platelets, kidney, lung, and cerebellum. The effect of tadalafil is more potent on PDE5 than on other phosphodiesterases. 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. 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. 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.

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, tadalafil significantly improved the erectile function leading to a mean per-subject proportion of successful attempts in patients treated with 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 (tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, 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 of patients 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 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 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 tadalafil 40 mg alone (n=37).

The proportion of patients with improvement in WHO functional class by week 16 was similar in the 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 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 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 tadalafil and with adverse events (AEs) expected in 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

Tadalafil is readily absorbed after oral administration and the mean maximum observed plasma concentration (C_{max}) 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 tadalafil is 2.5 L/h and the mean half-life is 17.5 hours in healthy subjects. 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 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 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 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 tadalafil, resulting in 25 % 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 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, C_{max} was 41 % higher than that observed in healthy subjects. Haemodialysis contributes negligibly to tadalafil elimination.

Due to increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to 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 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 tadalafil is prescribed once-a-day, a careful individual benefit/risk evaluation should be undertaken by the prescribing physician.

Patients with diabetes

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 tadalafil have been identified. No dose adjustment is warranted.

Gender

In healthy female and male subjects following single and multiple-doses of tadalafil, no clinically 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Croscarmellose sodium

Low Substituted Hydroxypropyl Cellulose

Microcrystalline Cellulose

Colloidal Silicone Dioxide 200

Sodium LaurylSulfate

Magnesium stearate

Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30^{o}C

6.5 Nature and contents of container

The caplets are packed in ALU/PVC blisters.
Pack sizes: 2 X 15 caplets

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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