

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lafaval 20 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg tadalafil.

Excipient with known effect:

Each 20 mg tablet contains 312.5 mg of lactose and 2.8 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Yellow colored, caplet shaped, biconvex, film-coated tablet, debossed with “T 20” on one side and plain on the other, with nominal dimensions 13.5 mm x 6.6 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Product Name] 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

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

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 [Product Name] is not recommended (see sections 4.4 and 5.2).

Hepatic impairment

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 [Product Name] 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 [Product Name] is not recommended (see sections 4.4 and 5.2).

Paediatric population

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

Method of administration

[Product Name] is for oral use.

4.3 Contraindications

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

Acute myocardial infarction within the last 90 days.

Severe hypotension (<90/50 mm Hg).

- 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 [Product Name] to patients who are using any form of organic nitrate is contraindicated (see section 4.5).

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).

Patients who have loss of vision in one eye because of non-arteritic anterior ischemic optic neuropathy (NAION), regardless of whether this episode was in connection or not with previous PDE5 inhibitor exposure (see section 4.4).

4.4 Special warnings and precautions for use

Cardiovascular

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 tadalafil in these patients, the use of [Product Name] 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 [Product Name] 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 alpha1 blockers concomitant administration of tadalafil may lead to symptomatic hypotension in some patients (see section 4.5). Therefore, the combination of [Product Name] 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. The patient should be advised that in case of sudden visual defect, to consult a physician immediately (see section 4.3). Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical studies, and use in these patients is not recommended.

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, previous hearing loss history and associated connective tissue diseases) patients should be advised to 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, [Product Name] is not recommended in patients with severe renal impairment.

Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and, therefore, dosing of [Product Name] is not recommended.

Priapism and anatomical deformation of the penis

Priapism has been reported in men treated with PDE5 inhibitors. 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.

[Product Name] 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

For patients chronically taking potent inducers of CYP3A4, such as rifampicin, the use of tadalafil is not recommended (see section 4.5).

For patients taking concomitant potent inhibitors of CYP3A4, such as ketoconazole or ritonavir, the use of tadalafil is not recommended (see section 4.5).

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. Patients should be informed not to take [Product Name] with these medicinal products.

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.

Bosentan

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

Lactose

[Product Name] contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicine 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

Effects of other substances on tadalafil

Cytochrome P450 Inhibitors

Azole Antifungals (e.g. ketoconazole)

Ketoconazole (200 mg daily), increased tadalafil (10 mg) single dose 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) single dose exposure (AUC) 4-fold and C_{max} by 22 %.

Protease inhibitors (e.g. ritonavir)

Ritonavir (200 mg twice daily), which is an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil (20 mg) single dose 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 C_{max} by 30 %.

Cytochrome P450 Inducers

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 C_{max} 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 C_{max}) of bosentan or its metabolites.

The safety and efficacy of combinations of tadalafil and other endothelin-1 receptor antagonists have not been studied.

Antimicrobial medicinal products (e.g. rifampicin)

A CYP3A4 inducer, rifampicin (600 mg daily), reduced tadalafil AUC by 88 % and C_{max} by 46 %, relative to the AUC and C_{max} values for tadalafil alone (10 mg).

Effects of tadalafil on other medicinal products

Nitrates

In clinical studies, tadalafil (5, 10 and 20 mg) was shown to augment the hypotensive effects of nitrates. This interaction lasted for more than 24 hours and was no longer detectable when 48 hours had elapsed after the last tadalafil dose. Therefore, administration of [Product Name] to patients who are using any form of organic nitrate is contraindicated (see section 4.3).

Anti-hypertensives (including Calcium channel blockers)

The co-administration of doxazosin (4 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 twelve 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.

In clinical pharmacology studies, the potential for tadalafil (10 and 20 mg) to augment the hypotensive effects of antihypertensive medicinal products was examined. Major classes of antihypertensive medicinal products were studied either as monotherapy or as part of combination therapy. In patients taking multiple antihypertensive medicinal products whose hypertension was not well controlled, greater reductions in blood

pressure were observed compared to patients whose blood pressure was well controlled, where the reduction was minimal and similar to that in healthy subjects. In patients receiving concomitant antihypertensive medicinal products, tadalafil 20 mg may induce a blood pressure decrease, which (with the exception of doxazosin - see above) is, in general, minor and not likely to be clinically relevant.

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).

Alcohol

Alcohol concentrations were not affected by co-administration with tadalafil (10 mg or 20 mg). In addition, no changes in tadalafil concentrations were seen after co-administration with 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. The effect of alcohol on cognitive function was not augmented by tadalafil (10 mg).

CYP1A2 substrates (e.g. theophylline)

When tadalafil 10 mg was administered with theophylline (a non-selective phosphodiesterase inhibitor) there was no pharmacokinetic interaction. The only pharmacodynamic effect was a small (3.5 bpm) increase in heart rate.

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.

Acetylsalicylic acid

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

P-glycoprotein substrates (e.g. digoxin)

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

Oral contraceptive pill

At steady-state, tadalafil (40 mg once per day) increased ethinylestradiol exposure (AUC) by 26 % and C_{max} 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 C_{max} 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.

4.6 Fertility, 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 [Product Name] during pregnancy.

Breastfeeding

Available pharmacodynamic/toxicological data in animals have shown excretion of tadalafil in milk.

A risk to the breastfed child cannot be excluded. [Product Name] 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 [Product Name], before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions, occurring in $\geq 10\%$ of patients in the tadalafil 40 mg treatment arm, were headache, nausea, back pain, dyspepsia, flushing, myalgia, nasopharyngitis 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

System organ class	Frequency	Preferred Term
<i>Immune system disorders</i>	Common	Hypersensitivity reactions ⁵
	Not known ¹	Angioedema
<i>Nervous system disorders</i>	Very common	Headache ⁶
	Common	Syncope, Migraine ⁵
	Uncommon	Seizures ⁵ , Transient amnesia ⁵
	Not known ¹	Stroke ² (including haemorrhagic events)
<i>Eye disorders</i>	Common	Blurred vision
	Not known ¹	Non-arteritic anterior ischemic optic neuropathy (NAION), Retinal vascular occlusion, Visual field defect
<i>Ear and labyrinth disorders</i>	Uncommon	Tinnitus
	Not known ¹	Sudden hearing loss
<i>Cardiac disorders</i>	Common	Palpitations ^{2,5}
	Uncommon	Sudden cardiac death ^{2,5} , Tachycardia ^{2,5}
	Not known ¹	Unstable angina pectoris, Ventricular arrhythmia, Myocardial Infarction ²
<i>Vascular disorders</i>	Very common	Flushing
	Common	Hypotension
	Uncommon	Hypertension
<i>Respiratory, thoracic and mediastinal disorders</i>	Very common	Nasopharyngitis (including nasal congestion, sinus congestion and rhinitis)
	Common	Epistaxis
<i>Gastrointestinal disorders</i>	Very common	Nausea, Dyspepsia (including abdominal pain/discomfort ³)

	Common	Vomiting, Gastroesophageal reflux
<i>Skin and subcutaneous tissue disorders</i>	Common	Rash
	Uncommon	Urticaria ⁵ , Hyperhidrosis (sweating) ⁵
	Not known ¹	Stevens-Johnson Syndrome, Exfoliative dermatitis
<i>Musculoskeletal, connective tissue and bone disorders</i>	Very common	Myalgia, Back pain, Pain in extremity (including limb discomfort)
<i>Renal and urinary disorders</i>	Uncommon	Haematuria
<i>Reproductive system and breast disorders</i>	Common	Increased uterine bleeding ⁴
	Uncommon	Priapism ⁵ , Penile haemorrhage, Haemospermia
	Not known ¹	Prolonged erections
<i>General disorders and administration site conditions</i>	Common	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 the national reporting system listed in Appendix V. [To be completed nationally]

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 with erectile dysfunction. Adverse reactions 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 potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). 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

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.

Additionally, improvements compared to placebo were observed with tadalafil 40 mg in the physical functioning, role-physical, bodily pain, general health, vitality and social functioning domains of the SF-36. No improvements were observed in the role emotional and mental health domains of the SF-36. Improvements compared to placebo were observed with tadalafil 40 mg in the EuroQol (EQ-5D) US and UK index scores comprising mobility, self-care, usual activities, pain/discomfort, anxiety/depression components, and in the visual analogue scale (VAS).

Cardiopulmonary hemodynamics was performed in 93 patients. Tadalafil 40 mg increased cardiac output (0.6 L/min) and reduced pulmonary artery pressures (-4.3 mmHg) and pulmonary vascular resistance (-209 dyn.s/cm⁵) compared to baseline ($p<0.05$). However, post hoc analyses demonstrated that changes from baseline in cardiopulmonary hemodynamic parameters for the tadalafil 40 mg treatment group were not significantly different compared to placebo.

Long-term treatment

357 patients from the placebo-controlled study entered a long-term extension study. Of these, 311 patients had been treated with tadalafil for at least 6 months and 293 for 1 year (median exposure 365 days; range 2 days to 415 days). For those patients for which there are data, the survival rate at 1 year is 96.4 %. Additionally, 6 minute walk

distance and WHO functional class status appeared to be stable in those treated with tadalafil for 1 year.

Tadalafil 20 mg administered to healthy subjects produced no significant difference compared to placebo in supine systolic and diastolic blood pressure (mean maximal decrease of 1.6/0.8 mm Hg, respectively), in standing systolic and diastolic blood pressure (mean maximal decrease of 0.2/4.6 mm Hg, respectively), and no significant change in heart rate.

In a study to assess the effects of tadalafil on vision, no impairment of colour discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test. This finding is consistent with the low affinity of tadalafil for PDE6 compared to PDE5. Across all clinical studies, reports of changes in colour vision were rare (< 0.1 %).

Three studies were conducted in men to assess the potential effect on spermatogenesis of tadalafil 10 mg (one 6-month study) and 20 mg (one 6-month and one 9-month study) administered daily. In two of these studies decreases were observed in sperm count and concentration related to tadalafil treatment of unlikely clinical relevance. These effects were not associated with changes in other parameters such as motility, morphology and FSH.

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 deferred the obligation to submit the results of studies with ADCIRCA 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 4 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 [Product Name] 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 77 l at steady state, 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 3.4 l/h at steady state and the mean terminal half-life is 16hours 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 to 20 mg, tadalafil 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

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 C_{max} 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 after a 10 mg dose. 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 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. If tadalafil is 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 tadalafil to patients with hepatic impairment.

Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied and therefore dosing of tadalafil in these patients is not recommended.

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 active substance 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

Tablet core

Lactose
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hydroxypropylcellulose (E463)
Polysorbate 80 (E433)
Magnesium stearate

Coating

Hypromellose 2910 (E464)
Lactose monohydrate
Titanium dioxide (E171)
Triacetin (E1518)
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters in cartons of 28, 30, 56 and 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Geneparm S.A.

18th Km Marathonos Avenue
Pallini 15351
Griekenland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 129720

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

Datum van eerste verlening van de vergunning: 2 november 2023

10. DATE OF REVISION OF THE TEXT