SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Avarante Prescription Free 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg tadalafil.

Excipient with known effect

Each film-coated tablet contains 119 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

A light yellow, round, biconvex film-coated tablet, debossed with 'M' on one side of the tablet and 'TL3' on the other side. The diameter of the tablet is approximately 8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult males.

In order for tadalafil to be effective, sexual stimulation is required.

Avarante Prescription Free is not indicated for use by women.

4.2 Posology and method of administration

Posology

The recommended dose is one 10 mg tablet taken at least 30 minutes prior to anticipated sexual activity.

The maximum dosing frequency is once per day.

Avarante Prescription Free 10 mg tablets are not recommended for continuous daily use. Men who anticipate using this medicinal product frequently (i.e., at least twice weekly) should be advised to consult their physician to discuss whether a once daily regimen with the lowest doses of tadalafil would be more suitable.

Patients should be advised that they may need to take Avarante Prescription Free a number of times on different occasions (a maximum of one 10 mg tablet per day), before they can achieve a penile erection satisfactory for sexual activity. Patients in whom tadalafil 10 mg does not produce an adequate effect should consult their physician.

Special populations

Elderly
Dose adjustments are not required in elderly patients.

Renal impairment
Dose adjustments are not required in patients with mild or moderate renal impairment. For patients with severe renal impairment, 10 mg is the maximum recommended dose. Patients with severe renal impairment (including those undergoing haemodialysis) should consult their physician before taking Avarante Prescription Free (see sections 4.4 and 5.2).

Hepatic impairment
The recommended dose of Avarante Prescription Free is 10 mg. Dose adjustments are not required in patients with mild or moderate hepatic impairment.

There is limited clinical data on the safety of tadalafil in patients with severe hepatic impairment (Child-Pugh class C). Patients with severe hepatic impairment should consult their physician before taking Avarante Prescription Free. There are no available data about the administration of doses higher than 10 mg of tadalafil to patients with hepatic impairment (see section 4.4 and 5.2).

Patients with diabetes
Dose adjustments are not required in people with diabetes.

Paediatric population
Avarante Prescription Free is not indicated for individuals below 18 years of age.

Method of administration

For oral use. Avarante Prescription Free may be taken with or without food.

4.3 Contraindications

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

Consistent with its known effects on the nitric oxide/cyclic guanosine monophosphate (cGMP) pathway (see section 5.1), tadalafil was shown to potentiate the hypotensive effects of nitrates, and its co-administration with nitric oxide donors (such as amyl nitrite, nicorandil or molsidomine) or nitrates in any form is therefore contraindicated (see section 4.5).

Avarante Prescription Free must not be used in men with cardiac disease for whom sexual activity is inadvisable (see section 4.4).

Avarante Prescription Free is contraindicated in the following groups of patients with cardiovascular disease, who were not included in clinical studies:
- 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 (< 90/50 mm Hg), or uncontrolled hypertension,
- patients with a stroke within the last 6 months.

Avarante Prescription Free 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).

Avarante Prescription Free is not indicated for use by women.
Avarante Prescription Free is not indicated for men without erectile dysfunction.
Avarante Prescription Free is not indicated for men under 18 years of age.

4.4 Special warnings and precautions for use

Patients should be advised that erection problems can be a sign of another medical condition such as heart disease, hypertension, diabetes or depression. Patients should also be advised that there is a degree of cardiac risk associated with sexual activity. All men with erectile dysfunction should consult their physician at the earliest opportunity for a clinical review of potential underlying conditions and risk factors associated with erectile dysfunction (ED).

Patients should consult their physician if symptoms of ED have not improved after taking Avarante Prescription Free on several consecutive occasions, or if their erectile dysfunction worsens.

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 or nitric oxide donors (see section 4.3 and 4.5).

It is not known if Avarante Prescription Free is effective in patients who have undergone pelvic surgery or radical non nerve sparing prostatectomy.

Cardiovascular

Patients with pre-existing cardiovascular disease and/or risk factors should be advised of the potential cardiac risk associated with sexual activity.

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, unstable angina pectoris, ventricular arrhythmia, stroke, transient ischemic attacks, chest pain, palpitations and tachycardia, have been reported either post marketing and/or in clinical studies. 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 Avarante Prescription Free, to sexual activity, or to a combination of these or other factors.

Use with alpha-1 adrenergic blockers

In patients who are taking alpha-1 blockers, concomitant administration of Avarante Prescription Free may lead to symptomatic hypotension in some patients (see section 4.5). The combination of tadalafil and doxazosin is not recommended.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR), and cases of NAION have been reported in connection with the intake of tadalafil and other PDE5 inhibitors. Most cases of CSCR resolved spontaneously after stopping tadalafil. Regarding NAION, 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, visual acuity impairment and/or visual distortion, 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 Avarante Prescription Free and seek prompt medical attention in the event of sudden decrease or loss of hearing (see section 4.8).

Renal and hepatic impairment

Patients with severe renal impairment (including those undergoing haemodialysis), could have increased tadalafil exposure (AUC), therefore, a physician should be consulted (see section 4.2 and 5.2).

There is limited clinical data on the safety of single dose administration of tadalafil in patients with severe hepatic insufficiency (Child Pugh class C).

Therefore, patients with severe hepatic impairment should consult their physician before taking Avarante Prescription Free.

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.

If a patient has an anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia), a physician should be consulted before taking Avarante Prescription Free.

Use with CYP3A4 inhibitors

Increased tadalafil exposure (AUC) has been observed with combined use of tadalafil and potent CYP3A4 inhibitors. Patients taking potent CYP3A4 inhibitors including ritonavir, saquinavir, ketoconazole, itraconazole, and erythromycin should be advised to consult a physician before taking Avarante Prescription Free (see section 4.5).

Patients should avoid drinking grapefruit juice (see section 4.5).

Avarante Prescription Free 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 Avarante Prescription Free in such combinations.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated 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 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}. 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. Patients taking potent CYP3A4 inhibitors should be advised to consult a physician before taking Avarante Prescription Free (see section 4.4).

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.

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.

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. Therefore, administration of Avarante Prescription Free 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 receiving 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 using any dose of tadalafil, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should have elapsed after the last dose of Avarante Prescription Free before nitrate administration is considered.

In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring.

Nicorandil and Molsidomine (nitric oxide donors)
Nicorandil and molsidomine have a mechanism of action similar to nitrates and thus have the potential for hypotensive effects similar to nitrates and are therefore contraindicated (see section 4.3).

Use with alpha-1 adrenergic 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 doxazosin in a significant manner. This effect lasts at least twelve hours and may be symptomatic, including syncope. The concomitant treatment with tadalafil and doxazosin 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-1 adrenergic blockers, and notably in the elderly. It is advisable for the patient to consult their physician before taking Avarante Prescription Free if they are taking other alpha-1 adrenergic blockers.

Use with anti-hypertensives
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 -see above-) is, in general, minor and not likely to be clinically relevant. Analysis of phase 3 clinical study 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 study 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, the patient should be advised to consult a physician before taking Avarante Prescription Free.

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.

Ethinylestradiol and terbutaline
Tadalafil has been demonstrated to produce an increase in the oral bioavailability of ethinylestradiol; a similar increase may be expected with oral administration of terbutaline, although the clinical consequence of this 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 maximize 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.

Acetylsalicylic acid
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 Fertility, pregnancy and lactation

Avarante Prescription Free is not indicated for use by women.

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 Avarante Prescription Free during pregnancy.

Breastfeeding

Available pharmacodynamics/toxicological data in animals have shown excretion of tadalafil in milk. A risk to the suckling child cannot be excluded. Avarante Prescription Free should not be used during breastfeeding.

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

Avarante Prescription Free 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 studies was similar, patients should be aware of how they react to Avarante Prescription Free, before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

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-aday dosing are experienced within the first 10 to 30 days of starting treatment.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical studies (comprising a total of 8 022 patients on tadalafil and 4 422 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).

Common	**Uncommon**	**Rare**	**Not known**
Immune system disorders			
	Hypersensitivity reactions	Angioedema[2]	
Nervous system disorders			
Headache	Dizziness	Stroke[1] (including haemorrhagic events), Syncope, Transient ischaemic attacks[1], Migraine[2], Seizures[2], Transient amnesia	
Eye disorders			
	Blurred vision, Sensations described as eye pain	Visual field defect, Swelling of eyelids, Conjunctival hyperaemia, Non-arteritic anterior ischemic optic neuropathy (NAION)[2], Retinal vascular occlusion[2]	Central serous chorioretinopathy
Ear and labyrinth disorders			
	Tinnitus	Sudden hearing loss	
Cardiac disorders[1]			
	Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris[2], Ventricular 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-Johnson syndrome[2], Exfoliative dermatitis[2],	

Common	Uncommon	Rare	Not known
		Hyperhydrosis (sweating)	
Musculoskeletal, connective tissue and bone 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 pain[1], Peripheral oedema, Fatigue	Facial oedema[2], Sudden cardiac 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 studies.
[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 studies, either for the treatment of erectile dysfunction or the treatment of benign prostatic hyperplasia, are limited. In clinical studies 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 studies 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.

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 ADR reporting system at www.medicinesauthority.gov.mt/adrportal

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). 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 absence of sexual stimulation.

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

Three clinical studies were conducted in 1 054 patients in an at-home setting to define the period of responsiveness to tadalafil on demand. 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 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.

Tadalafil at doses of 2 to 100 mg has been evaluated in 16 clinical studies involving 3 250 patients, including patients with erectile dysfunction of various severities (mild, moderate, severe), aetiologies, 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 or 20 mg flexible-dose, on demand) of 48 % as compared to 17 % with placebo.

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 with the reference medicinal product containing tadalafil in all subsets of the paediatric population in the treatment of the erectile dysfunction (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 Avarante Prescription Free may be taken with or without food. The time of dosing (morning versus evening) had no clinically relevant effects on the rate and extent of absorption.

Distribution

The mean volume of distribution is approximately 63 l, 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

Tadalafil pharmacokinetics in healthy subjects are linear with respect to time and dose. Over a dose range of 2.5 to 20 mg, exposure (AUC) increases proportionally with dose. Steady-state plasma concentrations are attained within 5 days of once-daily dosing.

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

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 impairment
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.

Hepatic impairment
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). If Avarante Prescription Free 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 diabetes
Tadalafil exposure (AUC) in patients with diabetes was approximately 19 % lower than the AUC value for healthy subjects. This difference in exposure does not warrant a dose adjustment.

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 1 000 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. Also see section 5.1.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Povidone (K-25)
Sodium lauryl sulfate
Poloxamer
Lactose
Microcrystalline cellulose
Croscarmellose sodium
Anhydrous colloidal silica
Magnesium stearate

Film-coating

Lactose
Hypromellose (15cP)
Titanium dioxide (E 171)
Iron oxide yellow (E 172)
Triacetin

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

PVC/PE/PVdC-Aluminium blisters in packs of 2, 4 or 8 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

Viatris Limited,
Damastown Industrial Park
Dublin 15, DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

MA1485/02301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th April 2025

10. DATE OF REVISION OF THE TEXT

7th April 2025