

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Avarante 10 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg tadalafil.

Excipient with known effect:

Each film-coated tablet contains 118.96 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

A light yellow, film-coated, round, biconvex tablet (8.1 ± 0.3 mm) debossed with 'M' on one side of the tablet and 'TL3' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Avarante 10 mg film-coated tablets are indicated in adult men with erectile dysfunction, which is the inability to achieve or maintain a penile erection sufficient for satisfactory sexual activity.

In order for Avarante 10 mg film-coated tablets to be effective, sexual stimulation is required.

4.2 Posology and method of administration

Posology

Use in adult men.

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

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

Avarante 10 mg film-coated tablets may be taken with or without food. The maximum dose frequency is once per day.

Most men will achieve an erection the first or second time they use Avarante 10 mg film-coated tablets. However, patients should be advised that they may need to take Avarante 10 mg film-coated tablets 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. If after several attempts on different dosing occasions patients are still not able to achieve a penile erection sufficient for satisfactory sexual activity, they should be advised to consult a physician.

Special populations

Elderly men

Dose adjustments are not required in elderly patients.

Men with renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment. Patients with severe renal impairment (including those undergoing haemodialysis) should consult their physician before taking Avarante 10 mg film-coated tablets (see section 4.4).

Men with hepatic impairment

Dose adjustments are not required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment should consult their physician before taking Avarante 10 mg film-coated tablets (see section 4.4).

Men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

Avarante 10 mg film-coated tablets are not indicated for individuals below 18 years of age.

Use in patients taking other medicinal products

Tadalafil is predominantly metabolised by the cytochrome P450 (CYP) 3A4 isoform. Tadalafil exposure is increased with CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, erythromycin, clarithromycin, cimetidine and grapefruit juice). Patients receiving concomitant treatment with CYP3A4 inhibitors should consult their physician before taking Avarante 10 mg film-coated tablets as a lower dose of tadalafil (2.5 mg or 5 mg on a once daily basis) may be more suitable (see sections 4.4 and 4.5).

In order to minimise the potential of developing postural hypotension in patients receiving alpha blocker treatment (e.g. alfuzosin, doxazosin or

tamsulosin), patients should be stabilised on alpha blocker therapy prior to initiating tadalafil treatment in the pharmacy setting. Patients receiving concomitant treatment with alpha blockers should consult their physician before taking Avarante 10 mg film-coated tablets as a lower dose of tadalafil (2.5 mg or 5 mg on a once daily basis) may be more suitable (see sections 4.4 and 4.5).

Method of administration

For oral use.

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 also known as “poppers”, nicorandil or molsidomine) or nitrates in any form is therefore contraindicated (see section 4.5).

Avarante 10 mg film-coated tablets must not be used in men with cardiac disease for whom sexual activity is inadvisable (see section 4.4).

Avarante 10 mg film-coated tablets are contraindicated in the following groups of patients with cardiovascular disease, who were not included in clinical trials:

- 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 10 mg film-coated tablets are 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 10 mg film-coated tablets should not be used in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease).

Avarante 10 mg film-coated tablets are not indicated for use by women.

Avarante 10 mg film-coated tablets are not intended for men without erectile dysfunction.

Avarante 10 mg film-coated tablets are not intended for men under 18 years of age.

4.4 Special warnings and precautions for use

Patients are advised that erection problems can be a sign of another medical condition such as heart disease, hypertension, diabetes or depression. As a result, all men with erectile dysfunction should be advised to consult their physician within 6 months for a clinical review of potential underlying conditions and risk factors associated with erectile dysfunction (ED). If symptoms of ED have not improved after taking Avarante 10 mg film-coated tablets on several consecutive occasions, or if their erectile dysfunction worsens, patients should be advised to consult their physician.

Patients who have undergone pelvic surgery or radical non nerve sparing prostatectomy should be advised to consult their physician as it is not known if Avarante 10 mg film-coated tablets are effective in these patients.

Patients with known hereditary degenerative retinal disorders such as retinitis pigmentosa should be advised to consult their physician as it is not known if Avarante 10 mg film-coated tablets are safe in these sub-groups of patients.

Cardiovascular

Patients with cardiovascular disease and/or risk factors should be informed that sexual activity could carry a cardiac risk.

Patients who experience chest pain during sexual activity should be advised to refrain from further sexual activity and seek medical attention immediately.

Agents for the treatment of erectile dysfunction, including tadalafil, are not recommended to be used by those men who with light or moderate physical activity, such as walking briskly for 20 minutes or climbing 2 flights of stairs, feel very breathless or experience chest pain. The following patients are considered at low cardiovascular risk from sexual activity: patients who have been successfully revascularised (e.g. via coronary artery bypass grafting, stenting, or angioplasty), patients with asymptomatic controlled hypertension, and those with mild valvular disease. These patients may be suitable for treatment but should consult a doctor before resuming sexual activity.

Patients previously diagnosed with the following must be advised to consult with their doctor before resuming sexual activity: uncontrolled hypertension,

moderate to severe valvular disease, left ventricular dysfunction, hypertrophic obstructive and other cardiomyopathies, or significant arrhythmias.

Tadalafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 5.1). Patients with increased susceptibility to vasodilators include those with left ventricular outflow obstruction (e.g., aortic stenosis), or those with the rare syndrome of multiple system atrophy manifesting as severely impaired autonomic control of blood pressure. Men with these conditions must not use the product without consulting a doctor.

Tadalafil potentiates the hypotensive effect of nitrates or nitric oxide donors (see section 4.3).

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 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 Avarante 10 mg film-coated tablets, to sexual activity, or to a combination of these or other factors.

Use with alpha blockers

In some patients who are taking alpha blockers, concomitant administration of Avarante 10 mg film-coated tablets may lead to symptomatic hypotension (see section 4.5). The concomitant treatment with tadalafil and doxazosin is not recommended.

Patients should not take Avarante 10 mg film-coated tablets in combination with doxazosin without first having talked to a physician.

In addition, it is advisable for the patient to check with the physician before taking Avarante 10 mg film-coated tablets if they are taking other alpha blockers (used for benign prostatic hypertrophy or hypertension).

Treatment should be stopped if symptoms of postural hypotension occur, and patients should seek advice from their doctor on what to do.

Vision

Visual defects, including Central Serous Chorioretinopathy (CSCR) and cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported in connection with the intake of Avarante 10 mg film-coated tablets 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 Avarante 10 mg film-coated tablets and seek medical attention 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 10 mg film-coated tablets 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 hemodialysis), could have increased tadalafil exposure (AUC), therefore, a physician should be consulted (see section 5.2).

There is limited clinical data on the safety of single dose administration of Avarante 10 mg film-coated tablets in patients with severe hepatic insufficiency (Child Pugh class C).

Therefore, patients with severe hepatic impairment should consult their physician before taking Avarante 10 mg film-coated tablets.

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.

Patients who have conditions which may predispose them to priapism (such as sickle cell anaemia, multiple myeloma or leukaemia), should consult a doctor before using agents for the treatment of erectile dysfunction, including tadalafil.

Avarante 10 mg film-coated tablets should not be used in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease)(see section 4.3).

Use with CYP3A4 inhibitors

Increased tadalafil exposure (AUC) has been observed with combined use of Avarante 10 mg film-coated tablets and potent CYP3A4 inhibitors. Patients taking potent CYP3A4 inhibitors (including ritonavir, saquinavir, ketoconazole, itraconazole, clarithromycin, and erythromycin) should be advised to consult a physician before taking Avarante 10 mg film-coated tablets (see section 4.5).

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

Avarante 10 mg film-coated tablets and other treatments for erectile dysfunction

The safety and efficacy of combinations of Avarante 10 mg film-coated tablets and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Use with alcohol

Drinking excessive alcohol can temporarily reduce a man's ability to get an erection. Men should be advised not to drink large amounts of alcohol before sexual activity.

Recreational drugs

Concurrent use of PDE5 inhibitors including tadalafil with recreational drugs (including but not limited to "poppers", nitrous oxide, GHB/GBL, methamphetamines, MDMA/ecstasy, ketamine, flunitrazepam, cannabis, opioids, cocaine, etc.) may lead to adverse events such as dizziness, decrease of blood pressure, stroke or heart attack, seizures, priapism, and coma.

Lactose content

Avarante 10 mg film-coated tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium content

Avarante 10 mg film-coated tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 10 mg film-coated tablets 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 Avarante 10 mg film-coated tablets, 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 10 mg film-coated tablets 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 alpha1 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 of 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. Patients should not take

Avarante in combination with doxazosin without first having talked to a physician(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, it is advisable for the patient to consult their physician before taking Avarante if they are taking other alpha 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 (bendroflumethiazide), 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 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, the patient should be advised to consult a physician before taking Avarante 10 mg film-coated tablets.

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. Patients being treated with theophylline should consult a physician before starting Avarante 10 mg film-coated tablets.

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 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.

Acetylsalicylic acid (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 Fertility, pregnancy and lactation

Avarante 10 mg film-coated tablets are 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).

Breastfeeding

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

A risk to the suckling child cannot be excluded.

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 10 mg film-coated tablets 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 Avarante 10 mg film-coated tablets before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in patients taking Avarante 10 mg film-coated tablets 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 Avarante 10 mg film-coated tablets. The adverse reactions reported were transient, and generally mild or moderate. The majority of headaches reported with Avarante 10 mg film-coated tablets 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 Avarante 10 mg film-coated tablets 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 ($\geq 1/10$), 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).

Very common	Common	Uncommon	Rare
<i>Immune system disorders</i>			
		Hypersensitivity reactions	Angioedema ²
<i>Nervous system disorders</i>			
	Headache	Dizziness	Stroke ¹ (including haemorrhagic events), Syncope, Transient ischaemic attacks ¹ , Migraine ² , Seizures ² , Transient amnesia
<i>Eye disorders</i>			
		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
<i>Ear and labyrinth disorders</i>			
		Tinnitus	Sudden hearing loss
<i>Cardiac disorders</i> ¹			

		Tachycardia, Palpitations	Myocardial infarction, Unstable angina pectoris ² , Ventricular arrhythmia ²
<i>Vascular disorders</i>			
	Flushing	Hypotension ³ , Hypertension	
<i>Respiratory, thoracic and mediastinal disorders</i>			
	Nasal congestion	Dyspnoea, Epistaxis	
<i>Gastrointestinal disorders</i>			
	Dyspepsia	Abdominal pain, Vomiting, Nausea, Gastro-oesophageal reflux,	
<i>Skin and subcutaneous tissue disorders</i>			
		Rash	Urticaria, Stevens-Johnson syndrome ² , Exfoliative dermatitis ² , Hyperhidrosis (sweating)
<i>Musculoskeletal, connective tissue and bone disorders</i>			
	Back pain, Myalgia, Pain in extremity		
<i>Renal and urinary disorders</i>			
		Haematuria	
<i>Reproductive system and breast disorders</i>			
		Prolonged erections	Priapism, Penile haemorrhage, Haematospermia
<i>General disorders and administration site conditions</i>			
		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 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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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

Two clinical studies were conducted in 706 patients in an at-home setting to define the period of responsiveness to tadalafil. 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 30 minutes following 10 mg 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 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 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 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 10 mg film-coated tablets 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 is 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 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.

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 Avarante 10 mg film-coated tablets in patients with severe hepatic insufficiency (Child-Pugh Class C). If Avarante 10 mg film-coated tablets 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 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

Tablet core:

Lactose, anhydrous
Poloxamer 188
Cellulose, microcrystalline (pH101)
Povidone (K-25)
Croscarmellose sodium
Magnesium stearate
Sodium laurilsulfate
Silica, colloidal anhydrous

Film-coat:

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Iron oxide yellow (E172)
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-Alu blisters.

Pack sizes of 2, 4 and 8 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

Viatrix Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 46302/0243

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/05/2023

10 DATE OF REVISION OF THE TEXT

05/11/2025