

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Spedra 50 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of avanafil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Pale yellow oval tablets, debossed with “50” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men.

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

4.2 Posology and method of administration

Posology

Use in adult men

The recommended dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity (see section 5.1). Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.

Special populations

Elderly (≥ 65 years old)

Dose adjustments are not required in elder patients. Limited data are available in elder patients aged 70 years or above.

Renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). Spedra is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.3 and 5.2). Patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min but < 80 mL/min) who were enrolled in phase 3 studies showed decreased efficacy compared to those with normal renal function.

Hepatic impairment

Spedra is contraindicated in patients with severe hepatic impairment (Child Pugh class C) (see sections 4.3 and 5.2). Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum efficacious dose and adjust posology based on tolerance.

Use in men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of Spedra in the paediatric population in the indication of erectile dysfunction.

Use in patients using other medicinal products

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is contraindicated (see sections 4.3, 4.4 and 4.5).

In patients receiving concomitant treatment with moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of avanafil should not exceed 100 mg, with an interval of at least 48 hours between doses (see section 4.5).

Method of administration

For oral use. If Spedra is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

4.3 Contraindications

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

Patients who are using any form of organic nitrate or nitric oxide donors (such as amyl nitrite) (see section 4.5).

The co-administration of type 5 phosphodiesterase (PDE5) inhibitors, including avanafil, with guanylate cyclase stimulators, such as riociguat is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease before prescribing Spedra.

The use of avanafil is contraindicated in:

- Patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

Patients with severe hepatic impairment (Child-Pugh C).

Patients with severe renal impairment (creatinine clearance < 30 mL/min).

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).

Patients with known hereditary degenerative retinal disorders.

Patients who are using potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

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

Cardiovascular status

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients since there is a degree of cardiac risk associated with sexual activity (see section 4.3). Avanafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 4.5), and as such potentiates the hypotensive effect of nitrates (see section 4.3). Patients with left ventricular outflow obstruction, e.g. aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators, including PDE5 inhibitors.

Priapism

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

Visual problems

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 PDE5 inhibitors. The patient should be advised that in case of sudden visual effects he should stop taking Spedra and consult a physician immediately (see section 4.3).

Effect on bleeding

In vitro studies with human platelets indicate that PDE5 inhibitors do not have an effect on platelet aggregation on their own, but at supratherapeutic doses they potentiate the anti-aggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, PDE5 inhibitors do not appear to affect bleeding time alone or in combination with acetylsalicylic acid.

There is no safety information on the administration of avanafil to patients with bleeding disorders or active peptic ulceration. Therefore, avanafil should be administered to such patients only after careful benefit-risk assessment.

Decreased or sudden loss of hearing

Patients should be advised to stop taking PDE5 inhibitors, including avanafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Concomitant use of alpha-blockers

The concomitant use of alpha-blockers and avanafil may lead to symptomatic hypotension in some patients due to additive vasodilatory effects (see section 4.5). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating Spedra. Patients who demonstrate haemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of avanafil.
- In those patients who are stable on alpha-blocker therapy, avanafil should be initiated at the lowest dose of 50 mg.
- In those patients already taking an optimised dose of Spedra, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking avanafil.

- The safety of combined use of avanafil and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medicinal products.

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent inhibitors of CYP3A4, such as ketoconazole or ritonavir is contraindicated (see sections 4.2, 4.3 and 4.5).

Concomitant use of other treatments for erectile dysfunction

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

Concomitant use of alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension (see section 4.5). Patients should be advised that concurrent use of avanafil and alcohol may increase the likelihood of hypotension, dizziness, or syncope. Physicians should also advise patients on what to do in the event of postural hypotensive symptoms.

Populations not studied

Avanafil has not been evaluated in patients with erectile dysfunction due to spinal cord injury or other neurological disorders and in subjects with severe renal or hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for pharmacodynamic interactions with avanafil

Nitrates

Avanafil was shown to augment the hypotensive effects of nitrates compared to placebo in healthy subjects. This is thought to result from the combined effects of nitrates and avanafil on the nitric oxide/cGMP pathway. Therefore, administration of avanafil to patients who are using any form of organic nitrate or nitric oxide donor (such as amyl nitrite) is contraindicated. In a patient who has taken avanafil within 12 hours, where nitrate administration is deemed medically necessary in a life-threatening situation, the likelihood of a significant and potentially dangerous drop in blood pressure is increased. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate haemodynamic monitoring (see section 4.3).

Medicinal products reducing systemic blood pressure

As a vasodilator, avanafil may reduce systemic blood pressure. If Spedra is used in combination with another medicinal product which reduces systemic blood pressure, the additive effects may result in symptomatic hypotension (e.g. dizziness, light-headedness, syncope or near-syncope). In phase III clinical trials no events of “hypotension” but occasional episodes of “dizziness” were observed (see section 4.8). One episode of “syncope” was observed in placebo and one episode on 100 mg of avanafil in phase III clinical trials.

Patients with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators including avanafil (see section 4.4).

Alpha-blockers

Haemodynamic interactions with doxazosin and tamsulosin were studied in healthy subjects in a two-period crossover-design trial. In patients receiving stable doxazosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 2.5 mmHg and 6.0 mmHg, respectively. In total, 7/24 subjects experienced values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

In patients receiving stable tamsulosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 3.6 mmHg and 3.1 mmHg,

respectively and 5/24 subjects experienced blood pressure values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

Antihypertensives other than alpha-blockers

A clinical study was conducted to assess the effect of avanafil on the potentiation of the blood pressure-lowering effects of selected antihypertensive medicinal products (amlodipine and enalapril). Results showed a mean maximum decrease in supine blood pressure of 2/3 mmHg compared to placebo with enalapril and 1/-1 mmHg with amlodipine when avanafil was co-administered. There was a statistically significant difference in maximum decrease from baseline in supine diastolic blood pressure with enalapril and avanafil only, which returned to baseline 4 hours after the dose of avanafil. In both cohorts, one subject experienced a decrease in blood pressure without symptoms of hypotension, which resolved within 1 hour of onset. Avanafil had no effect on the pharmacokinetics of amlodipine, but amlodipine increased the maximum and total exposure of avanafil by 28% and 60%, respectively (see section 4.4).

Alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension. In a single-dose three-way crossover design study evaluating healthy subjects, the mean maximum reduction in diastolic blood pressure was significantly greater following avanafil administered in combination with alcohol than following avanafil alone (3.2 mmHg) or alcohol alone (5.0 mmHg) (see section 4.4).

Other treatments for erectile dysfunction

The safety and efficacy of combinations of avanafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied (see section 4.4).

Effects of other substances on avanafil

Avanafil is a substrate of and predominantly metabolised by CYP3A4. Studies have shown that medicinal products that inhibit CYP3A4 can increase avanafil exposure (see section 4.2).

CYP3A4 Inhibitors

Ketoconazole (400 mg daily), a selective and highly potent inhibitor of CYP3A4, increased avanafil 50 mg single-dose C_{max} and exposure (AUC) equal to 3-fold and 14-fold respectively and prolonged the half-life of avanafil to approximately 9 hours. Ritonavir (600 mg twice daily), a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9, increased avanafil 50 mg single-dose C_{max} and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of avanafil to approximately 9 hours. Other strong inhibitors of CYP3A4 (e.g. itraconazole, voriconazole, clarithromycin, nefazodone, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) would be expected to have similar effects. Consequently, co-administration of avanafil with potent CYP3A4 inhibitors is contraindicated (see sections 4.2, 4.3 and 4.4).

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, increased avanafil 200 mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 8 hours. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) would be expected to have similar effects. Consequently, the maximum recommended dose of avanafil is 100 mg, not to exceed once every 48 hours for patients taking concomitant moderate CYP3A4 inhibitors (see section 4.2).

Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice would likely increase avanafil exposure. Patients should be advised to avoid grapefruit juice within 24 hours prior to taking avanafil.

CYP3A4 substrate

Amlodipine (5 mg daily) increased avanafil 200 mg single-dose C_{max} and AUC by approximately 28% and 60%, respectively. These exposure changes are not considered clinically significant. There was no effect of a single dose of avanafil on amlodipine plasma levels.

Although specific interactions of avanafil with rivaroxaban and apixaban (both CYP3A4 substrates) have not been studied, an interaction is not expected.

Cytochrome P450 Inducers

The potential effect of CYP inducers, especially inducers of CYP3A4 (e.g. bosentan, carbamazepine, efavirenz, phenobarbital and rifampicin) on the pharmacokinetics and efficacy of avanafil has not been evaluated. The concomitant use of avanafil and a CYP inducer is not recommended as it may decrease the efficacy of avanafil.

Effects of avanafil on other medicinal products

Cytochrome P450 Inhibition

In *in vitro* studies in human liver microsomes, avanafil showed a negligible potential for drug-drug interactions with CYP1A1/2, 2A6, 2B6 and 2E1. Further, the metabolites of avanafil (M4, M16 and M27), also demonstrated a minimal inhibition of CYPs 1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Based on these data avanafil is not anticipated to have a significant effect on other medicinal products metabolised by these enzymes.

Since the *in vitro* data identified potential avanafil interactions with CYPs 2C19, 2C8/9, 2D6 and 3A4, Update of section 4.8 of the SmPC in order to add 'Injection site amyloid deposits' to the list of adverse drug reactions (ADRs) with frequency not known, based on a review of the clinical study and post-marketing data to evaluate a possible causal association between anakinra (Kineret) and amyloidosis. The Package Leaflet is updated accordingly.

further clinical studies using omeprazole, rosiglitazone and desipramine did not reveal clinically relevant interactions with CYPs 2C19, 2C8/9 and 2D6.

Cytochrome P450 Induction

The potential induction of CYP1A2, CYP2B6 and CYP3A4 by avanafil evaluated in primary human hepatocytes *in vitro* did not reveal any potential interaction at clinically relevant concentrations.

Transporters

In vitro results showed for avanafil a modest potential for acting as P-gp substrate and P-gp inhibitor with digoxin as a substrate at concentrations lower than the calculated intestinal concentration. The potential of avanafil to interfere with the transport of other medicinal products mediated by P-gp is not known.

Based on *in vitro* data, at clinically relevant concentrations avanafil could be an inhibitor of BCRP. At clinically relevant concentrations avanafil is not an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 and BSEP.

The impact of avanafil on other transporters is unknown.

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has 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 avanafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

Spedra is not indicated for use in women.

There are no data from the use of avanafil 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).

Breast-feeding

There are no data on the use of avanafil during breast-feeding.

Fertility

There was no effect on sperm motility or morphology after single 200 mg oral doses of avanafil in healthy volunteers.

In a clinical trial performed in healthy volunteers and adult males with mild erectile dysfunction, the daily administration of avanafil 100 mg oral doses over a period of 26 weeks was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

4.7 Effects on ability to drive and use machines

Spedra has minor influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with avanafil, patients should be aware of how they react to Spedra before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Spedra is based on 2,566 subjects exposed to avanafil during the clinical development program. The most common adverse reactions reported in clinical studies were headache, flushing, nasal and sinus congestion and back pain. Overall adverse events and adverse reactions for avanafil-treated subjects were more frequent in subjects with a Body Mass Index (BMI) <25 (normal BMI subjects).

In the long term clinical study, the percentage of patients who experienced adverse reactions decreased with increasing length of exposure.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed in placebo-controlled clinical trials according to the MedDRA 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 available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Infections and infestations			Influenza Nasopharyngitis
Immune system disorders			Seasonal allergy
Metabolism and nutrition disorders			Gout
Psychiatric disorders			Insomnia Premature ejaculation Inappropriate affect
Nervous system disorders	Headache	Dizziness Somnolence Sinus headache	Psychomotor hyperactivity
Eye disorders		Vision blurred	
Cardiac disorders		Palpitations	Angina pectoris Tachycardia
Vascular disorders	Flushing	Hot flush	Hypertension

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Sinus congestion Dyspnoea exertional	Rhinorrhoea Upper respiratory tract congestion Epistaxis
Gastrointestinal disorders		Dyspepsia Nausea Vomiting Stomach discomfort	Dry mouth Gastritis Abdominal pain lower Diarrhoea
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal and connective tissue disorders		Back pain Muscle tightness	Flank pain Myalgia Muscle spasms
Renal and urinary disorders			Pollakiuria
Reproductive system and breast disorders			Penis disorder Spontaneous penile erection Pruritus genital
General disorders and administration site conditions		Fatigue	Asthenia Chest pain Influenza like illness Oedema peripheral
Investigations		Hepatic enzyme increased Electrocardiogram abnormal Heart rate increased	Blood pressure increased Blood urine present Cardiac murmur Prostate specific antigen increased Weight increased Blood bilirubin increased Blood creatinine increased Body temperature increased

Description of selected adverse reactions observed with other PDE5 inhibitors

Non-arteritic anterior ischaemic optic neuropathy (NAION) and sudden loss of hearing have been reported in a small number of postmarketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil (see section 4.4).

Priapism has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil.

Haematuria, haemospermia and penile haemorrhage has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors.

Hypotension has been reported post marketing with other PDE5 inhibitors, and dizziness, a symptom commonly caused by lowered blood pressure, has been reported in clinical trials with avanafil (see section 4.5).

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](#).

4.9 Overdose

Single dose of up to 800 mg of avanafil have been given to healthy subjects and multiple daily doses up to 300 mg have been given to patients. Adverse reactions were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as avanafil is highly bound to plasma proteins and it is not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals; Drugs used in erectile dysfunction.
ATC code: G04BE10.

Mechanism of action

Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that avanafil is highly selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (> 100-fold for PDE6; > 1,000-fold for PDE4, PDE8 and PDE10; > 5,000-fold for PDE2 and PDE7; > 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil is > 100-fold more potent for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. The approximately 20,000-fold selectivity for PDE5 versus PDE3, and enzyme found in heart and blood vessels, is important because PDE3 is involved in control of cardiac contractility.

In a penile plethysmography (RigiScan) study, avanafil 200 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 20 minutes after dosing and overall response of these subjects to avanafil was statistically significant, compared to placebo, in the 20-40 minute time interval.

Clinical efficacy and safety

In clinical trials, avanafil was assessed for its effect on the ability of men with erectile dysfunction (ED) to achieve and maintain an erection sufficient for satisfactory sexual activity. Avanafil was evaluated in 4 randomized, double-blind, placebo-controlled, parallel group trials of up to 3 months in duration in the general population with ED, in patients with Type 1 or Type 2 diabetes and ED, and in patients with ED following bilateral nerve-sparing radical prostatectomy. The fourth study investigated the onset of action of avanafil at two doses (100 and 200 mg) in terms of per-subject proportion of sexual attempts resulting in satisfactory completion of sexual intercourse. A total of 1774 patients received avanafil, which was taken as needed at doses of 50 mg (one study), 100 mg and 200 mg (four studies), respectively. Patients were instructed to take 1 dose of study medicinal product approximately 30 minutes prior to initiation of sexual activity. In the fourth study patients were

encouraged to attempt sexual intercourse approximately 15 minutes post-dosing, to assess the onset of the erectogenic effect of avanafil, taken on an as needed basis, at 100 and 200 mg dose.

In addition, a subset of patients was enrolled into an open-label extension trial with 493 patients receiving avanafil for at least 6 months and 153 patients for at least 12 months. Patients were initially assigned to avanafil 100 mg and at any point during the trial, they could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based on their individual response to treatment.

In all trials, statistically significant improvement in all primary efficacy measures were observed for all three doses of avanafil compared to placebo. These differences were maintained with long term treatment (as per studies in the general ED population, in diabetics with ED and in men with ED following bilateral nerve-sparing radical prostatectomy and in the open-label extension trial).

In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo.

In men with either Type 1 or Type 2 diabetes mellitus, the mean percentage of attempts resulting in successful intercourse was approximately 34% and 40% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 21% for the placebo group.

In men with ED following bilateral nerve-sparing radical prostatectomy, the mean percentage of attempts resulting in successful intercourse was approximately 23% and 26% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 9% for placebo.

In the Time to onset study, avanafil demonstrated statistically significant improvement in the primary efficacy variable (average per subject proportion of successful responses by time after dose administration, to the Sexual Encounter Profile 3 - SEP3) as compared with placebo, resulting in successful intercourse in 24.71% of the attempts for the 100 mg dose and 28.18% for the 200 mg dose at approximately 15 minutes after dosing compared to 13.78% for placebo.

Across all of the pivotal trials of avanafil, the percentage of successful intercourse attempts was significantly higher for all doses of avanafil compared to placebo for attempts at all post-dosing time intervals examined.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Spedra in all subsets of the paediatric population in erectile dysfunction (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4). The concomitant use of potent CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) is associated with increased plasma exposure of avanafil (see section 4.5). Avanafil has a terminal half-life of approximately 6-17 hours.

Absorption

Avanafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 0.5 to 0.75 hours of oral dosing in the fasted state. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There was no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance.

Distribution

Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total active substance concentrations, age, renal and hepatic function. Avanafil was not found to accumulate in plasma when dosed 200 mg twice daily over 7 days. Based upon measurements of avanafil in semen of healthy volunteers 45-90 minutes after dosing, less than 0.0002% of the administered dose may appear in the semen of patients.

Biotransformation

Avanafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite shows a phosphodiesterase selectivity profile similar to that of avanafil and an *in vitro* inhibitory potency for PDE5 18% of that of avanafil. Therefore, M4 accounts for approximately 4% of total pharmacologic activity. The M16 metabolite was inactive against PDE5.

Elimination

Avanafil is extensively metabolised in humans. After oral administration, avanafil is excreted as metabolites predominantly in the faeces (approximately 63% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose).

Other special populations

Elderly Older patients (65 years or over) had comparable exposure to that seen in younger patients (18-45 years). However, data on subjects older than 70 years are limited.

Renal impairment

In subjects with mild (creatinine clearance ≥ 50 - < 80 mL/min) and moderate (creatinine clearance ≥ 30 - < 50 mL/min) renal impairment, the pharmacokinetics of a single 200 mg dose of avanafil were not altered. There are no data available for subjects with severe renal insufficiency or end-stage renal disease on haemodialysis.

Hepatic impairment

Subjects with mild hepatic impairment (Child-Pugh A) had comparable exposure to subjects with normal hepatic function when a single dose of 200 mg avanafil was administered.

The exposure 4 hours post-dose was lower in subjects with moderate hepatic impairment (Child-Pugh B) compared to subject with normal hepatic function after 200 mg of avanafil. The maximum concentration and exposure was similar to that observed after subjects with normal hepatic function received an efficacious avanafil 100 mg dose.

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.

In a rat fertility and early embryonic development trial, a decrease in fertility and sperm motility, altered estrous cycles, and an increased percentage of abnormal sperm occurred at 1000 mg/kg/day, a dose which also caused parental toxicity in the treated males and females. No effects on fertility or sperm parameters were noted at doses up to 300 mg/kg/day (in male rats 9 times human exposure based on unbound AUC at a dose of 200 mg). There were no treatment-related testicular findings in mice or rats treated with doses up to 600 or 1000 mg/kg/day for 2 years, and no testicular findings in dogs treated with avanafil for 9 months at exposures 110 times human exposure at the Maximum Recommended Human Dose (MRHD).

In pregnant rats, no evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed at doses up to 300 mg/kg/day (approximately 15 times the MRHD on a mg/m² basis in a 60 kg subject). At a maternally toxic dose of 1000 mg/kg/day (approximately 49 times the MRHD on a mg/m² basis),

decreased fetal body weight occurred with no signs of teratogenicity. In pregnant rabbits, no teratogenicity, embryotoxicity or fetotoxicity was observed at doses up to 240 mg/kg/day (approximately 23 times the MRHD on a mg/m² basis. In the rabbit study, maternal toxicity was observed at 240 mg/kg/day.

In a rat pre- and post-natal development study, pups exhibited persistent decreases in body weight at 300 mg/kg/day and higher (approximately 15 times the MRHD on a mg/m² basis) and delayed sexual development at 600 mg/kg/day (approximately 29 times the MRHD on a mg/m² basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Fumaric acid
Hydroxypropylcellulose
Hydroxypropylcellulose, low substituted
Calcium carbonate
Magnesium stearate
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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/PCTFE/Aluminium or PVC/PVDC/Aluminium perforated unit dose blisters in cartons of 4x1, 8x1 and 12x1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare,
L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/001-003

EU/1/13/841/012-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 2013

Date of latest renewal: 23 April 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Spedra 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg of avanafil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Pale yellow oval tablets, debossed with “100” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men.

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

4.2 Posology and method of administration

Posology

Use in adult men

The recommended dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity (see section 5.1). Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.

Special populations

Elderly (≥ 65 years old)

Dose adjustments are not required in elder patients. Limited data are available in elder patients aged 70 years or above.

Renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). Spedra is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.3 and 5.2). Patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min but < 80 mL/min) who were enrolled in phase 3 studies showed decreased efficacy compared to those with normal renal function.

Hepatic impairment

Spedra is contraindicated in patients with severe hepatic impairment (Child Pugh class C) (see sections 4.3 and 5.2). Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum efficacious dose and adjust posology based on tolerance.

Use in men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of Spedra in the paediatric population in the indication of erectile dysfunction.

Use in patients using other medicinal products

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is contraindicated (see sections 4.3, 4.4 and 4.5).

In patients receiving concomitant treatment with moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of avanafil should not exceed 100 mg, with an interval of at least 48 hours between doses (see section 4.5).

Method of administration

For oral use. If Spedra is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

4.3 Contraindications

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

Patients who are using any form of organic nitrate or nitric oxide donors (such as amyl nitrite) (see section 4.5).

The co-administration of type 5 phosphodiesterase (PDE5) inhibitors, including avanafil, with guanylate cyclase stimulators, such as riociguat is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease before prescribing Spedra.

The use of avanafil is contraindicated in:

- Patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

Patients with severe hepatic impairment (Child-Pugh C).

Patients with severe renal impairment (creatinine clearance < 30 mL/min).

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).

Patients with known hereditary degenerative retinal disorders.

Patients who are using potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

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

Cardiovascular status

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients since there is a degree of cardiac risk associated with sexual activity (see section 4.3). Avanafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 4.5), and as such potentiates the hypotensive effect of nitrates (see section 4.3). Patients with left ventricular outflow obstruction, e.g. aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators, including PDE5 inhibitors.

Priapism

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

Visual problems

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 PDE5 inhibitors. The patient should be advised that in case of sudden visual effects he should stop taking Spedra and consult a physician immediately (see section 4.3).

Effect on bleeding

In vitro studies with human platelets indicate that PDE5 inhibitors do not have an effect on platelet aggregation on their own, but at supratherapeutic doses they potentiate the anti-aggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, PDE5 inhibitors do not appear to affect bleeding time alone or in combination with acetylsalicylic acid.

There is no safety information on the administration of avanafil to patients with bleeding disorders or active peptic ulceration. Therefore, avanafil should be administered to such patients only after careful benefit-risk assessment.

Decreased or sudden loss of hearing

Patients should be advised to stop taking PDE5 inhibitors, including avanafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Concomitant use of alpha-blockers

The concomitant use of alpha-blockers and avanafil may lead to symptomatic hypotension in some patients due to additive vasodilatory effects (see section 4.5). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating Spedra. Patients who demonstrate haemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of avanafil.
- In those patients who are stable on alpha-blocker therapy, avanafil should be initiated at the lowest dose of 50 mg.
- In those patients already taking an optimised dose of Spedra, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking avanafil.

- The safety of combined use of avanafil and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medicinal products.

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent inhibitors of CYP3A4, such as ketoconazole or ritonavir is contraindicated (see sections 4.2, 4.3 and 4.5).

Concomitant use of other treatments for erectile dysfunction

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

Concomitant use of alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension (see section 4.5). Patients should be advised that concurrent use of avanafil and alcohol may increase the likelihood of hypotension, dizziness, or syncope. Physicians should also advise patients on what to do in the event of postural hypotensive symptoms.

Populations not studied

Avanafil has not been evaluated in patients with erectile dysfunction due to spinal cord injury or other neurological disorders and in subjects with severe renal or hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for pharmacodynamic interactions with avanafil

Nitrates

Avanafil was shown to augment the hypotensive effects of nitrates compared to placebo in healthy subjects. This is thought to result from the combined effects of nitrates and avanafil on the nitric oxide/cGMP pathway. Therefore, administration of avanafil to patients who are using any form of organic nitrate or nitric oxide donor (such as amyl nitrite) is contraindicated. In a patient who has taken avanafil within 12 hours, where nitrate administration is deemed medically necessary in a life-threatening situation, the likelihood of a significant and potentially dangerous drop in blood pressure is increased. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate haemodynamic monitoring (see section 4.3).

Medicinal products reducing systemic blood pressure

As a vasodilator, avanafil may reduce systemic blood pressure. If Spedra is used in combination with another medicinal product which reduces systemic blood pressure, the additive effects may result in symptomatic hypotension (e.g. dizziness, light-headedness, syncope or near-syncope). In phase III clinical trials no events of “hypotension” but occasional episodes of “dizziness” were observed (see section 4.8). One episode of “syncope” was observed in placebo and one episode on 100 mg of avanafil in phase III clinical trials.

Patients with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators including avanafil (see section 4.4).

Alpha-blockers

Haemodynamic interactions with doxazosin and tamsulosin were studied in healthy subjects in a two-period crossover-design trial. In patients receiving stable doxazosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 2.5 mmHg and 6.0 mmHg, respectively. In total, 7/24 subjects experienced values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

In patients receiving stable tamsulosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 3.6 mmHg and 3.1 mmHg,

respectively and 5/24 subjects experienced blood pressure values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

Antihypertensives other than alpha-blockers

A clinical study was conducted to assess the effect of avanafil on the potentiation of the blood pressure-lowering effects of selected antihypertensive medicinal products (amlodipine and enalapril). Results showed a mean maximum decrease in supine blood pressure of 2/3 mmHg compared to placebo with enalapril and 1/-1 mmHg with amlodipine when avanafil was co-administered. There was a statistically significant difference in maximum decrease from baseline in supine diastolic blood pressure with enalapril and avanafil only, which returned to baseline 4 hours after the dose of avanafil. In both cohorts, one subject experienced a decrease in blood pressure without symptoms of hypotension, which resolved within 1 hour of onset. Avanafil had no effect on the pharmacokinetics of amlodipine, but amlodipine increased the maximum and total exposure of avanafil by 28% and 60%, respectively (see section 4.4).

Alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension. In a single-dose three-way crossover design study evaluating healthy subjects, the mean maximum reduction in diastolic blood pressure was significantly greater following avanafil administered in combination with alcohol than following avanafil alone (3.2 mmHg) or alcohol alone (5.0 mmHg) (see section 4.4).

Other treatments for erectile dysfunction

The safety and efficacy of combinations of avanafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied (see section 4.4).

Effects of other substances on avanafil

Avanafil is a substrate of and predominantly metabolised by CYP3A4. Studies have shown that medicinal products that inhibit CYP3A4 can increase avanafil exposure (see section 4.2).

CYP3A4 Inhibitors

Ketoconazole (400 mg daily), a selective and highly potent inhibitor of CYP3A4, increased avanafil 50 mg single-dose C_{max} and exposure (AUC) equal to 3-fold and 14-fold respectively and prolonged the half-life of avanafil to approximately 9 hours. Ritonavir (600 mg twice daily), a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9, increased avanafil 50 mg single-dose C_{max} and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of avanafil to approximately 9 hours. Other strong inhibitors of CYP3A4 (e.g. itraconazole, voriconazole, clarithromycin, nefazodone, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) would be expected to have similar effects. Consequently, co-administration of avanafil with potent CYP3A4 inhibitors is contraindicated (see sections 4.2, 4.3 and 4.4).

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, increased avanafil 200 mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 8 hours. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) would be expected to have similar effects. Consequently, the maximum recommended dose of avanafil is 100 mg, not to exceed once every 48 hours for patients taking concomitant moderate CYP3A4 inhibitors (see section 4.2).

Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice would likely increase avanafil exposure. Patients should be advised to avoid grapefruit juice within 24 hours prior to taking avanafil.

CYP3A4 substrate

Amlodipine (5 mg daily) increased avanafil 200 mg single-dose C_{max} and AUC by approximately 28% and 60%, respectively. These exposure changes are not considered clinically significant. There was no effect of a single dose of avanafil on amlodipine plasma levels.

Although specific interactions of avanafil with rivaroxaban and apixaban (both CYP3A4 substrates) have not been studied, an interaction is not expected.

Cytochrome P450 Inducers

The potential effect of CYP inducers, especially inducers of CYP3A4 (e.g. bosentan, carbamazepine, efavirenz, phenobarbital and rifampicin) on the pharmacokinetics and efficacy of avanafil has not been evaluated. The concomitant use of avanafil and a CYP inducer is not recommended as it may decrease the efficacy of avanafil.

Effects of avanafil on other medicinal products

Cytochrome P450 Inhibition

In *in vitro* studies in human liver microsomes, avanafil showed a negligible potential for drug-drug interactions with CYP1A1/2, 2A6, 2B6 and 2E1. Further, the metabolites of avanafil (M4, M16 and M27), also demonstrated a minimal inhibition of CYPs 1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Based on these data avanafil is not anticipated to have a significant effect on other medicinal products metabolised by these enzymes.

Since the *in vitro* data identified potential avanafil interactions with CYPs 2C19, 2C8/9, 2D6 and 3A4, further clinical studies using omeprazole, rosiglitazone and desipramine did not reveal clinically relevant interactions with CYPs 2C19, 2C8/9 and 2D6.

Cytochrome P450 Induction

The potential induction of CYP1A2, CYP2B6 and CYP3A4 by avanafil evaluated in primary human hepatocytes *in vitro* did not reveal any potential interaction at clinically relevant concentrations.

Transporters

In vitro results showed for avanafil a modest potential for acting as P-gp substrate and P-gp inhibitor with digoxin as a substrate at concentrations lower than the calculated intestinal concentration. The potential of avanafil to interfere with the transport of other medicinal products mediated by P-gp is not known.

Based on *in vitro* data, at clinically relevant concentrations avanafil could be an inhibitor of BCRP. At clinically relevant concentrations avanafil is not an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 and BSEP.

The impact of avanafil on other transporters is unknown.

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effect when PDE5 inhibitors were combined with riociguat. In clinical studies, riociguat has shown to augment the hypotensive effects of PDE 5 inhibitors. There was no evidence of favourable clinical effect of the combination in the population studied. Concomitant use of riociguat with PDE5 inhibitors, including avanafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

Spedra is not indicated for use in women.

There are no data from the use of avanafil 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).

Breast-feeding

There are no data on the use of avanafil during breast-feeding.

Fertility

There was no effect on sperm motility or morphology after single 200 mg oral doses of avanafil in healthy volunteers.

In a clinical trial performed in healthy volunteers and adult males with mild erectile dysfunction, the daily administration of avanafil 100 mg oral doses over a period of 26 weeks was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

4.7 Effects on ability to drive and use machines

Spedra has minor influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with avanafil, patients should be aware of how they react to Spedra before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Spedra is based on 2,566 subjects exposed to avanafil during the clinical development program. The most common adverse reactions reported in clinical studies were headache, flushing, nasal and sinus congestion and back pain. Overall adverse events and adverse reactions for avanafil-treated subjects were more frequent in subjects with a Body Mass Index (BMI) <25 (normal BMI subjects).

In the long term clinical study, the percentage of patients who experienced adverse reactions decreased with increasing length of exposure.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed in placebo-controlled clinical trials according to the MedDRA 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 available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Infections and infestations			Influenza Nasopharyngitis
Immune system disorders			Seasonal allergy
Metabolism and nutrition disorders			Gout
Psychiatric disorders			Insomnia Premature ejaculation Inappropriate affect
Nervous system disorders	Headache	Dizziness Somnolence Sinus headache	Psychomotor hyperactivity
Eye disorders		Vision blurred	
Cardiac disorders		Palpitations	Angina pectoris Tachycardia
Vascular disorders	Flushing	Hot flush	Hypertension
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Sinus congestion Dyspnoea exertional	Rhinorrhoea Upper respiratory tract congestion Epistaxis

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Gastrointestinal disorders		Dyspepsia Nausea Vomiting Stomach discomfort	Dry mouth Gastritis Abdominal pain lower Diarrhoea
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal and connective tissue disorders		Back pain Muscle tightness	Flank pain Myalgia Muscle spasms
Renal and urinary disorders			Pollakiuria
Reproductive system and breast disorders			Penis disorder Spontaneous penile erection Pruritus genital
General disorders and administration site conditions		Fatigue	Asthenia Chest pain Influenza like illness Oedema peripheral
Investigations		Hepatic enzyme increased Electrocardiogram abnormal Heart rate increased	Blood pressure increased Blood urine present Cardiac murmur Prostate specific antigen increased Weight increased Blood bilirubin increased Blood creatinine increased Body temperature increased

Description of selected adverse reactions observed with other PDE5 inhibitors

Non-arteritic anterior ischaemic optic neuropathy (NAION) and sudden loss of hearing have been reported in a small number of postmarketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil (see section 4.4).

Priapism has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil.

Haematuria, haemospermia and penile haemorrhage has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors.

Hypotension has been reported post marketing with other PDE5 inhibitors, and dizziness, a symptom commonly caused by lowered blood pressure, has been reported in clinical trials with avanafil (see section 4.5).

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](#).

4.9 Overdose

Single dose of up to 800 mg of avanafil have been given to healthy subjects and multiple daily doses up to 300 mg have been given to patients. Adverse reactions were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as avanafil is highly bound to plasma proteins and it is not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals: Drugs used in erectile dysfunction.
ATC code: G04BE10.

Mechanism of action

Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that avanafil is highly selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (> 100-fold for PDE6; > 1,000-fold for PDE4, PDE8 and PDE10; > 5,000-fold for PDE2 and PDE7; > 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil is > 100-fold more potent for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. The approximately 20,000-fold selectivity for PDE5 versus PDE3, and enzyme found in heart and blood vessels, is important because PDE3 is involved in control of cardiac contractility.

In a penile plethysmography (RigiScan) study, avanafil 200 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 20 minutes after dosing and overall response of these subjects to avanafil was statistically significant, compared to placebo, in the 20-40 minute time interval.

Clinical efficacy and safety

In clinical trials, avanafil was assessed for its effect on the ability of men with erectile dysfunction (ED) to achieve and maintain an erection sufficient for satisfactory sexual activity. Avanafil was evaluated in 4 randomized, double-blind, placebo-controlled, parallel group trials of up to 3 months in duration in the general population with ED, in patients with Type 1 or Type 2 diabetes and ED, and in patients with ED following bilateral nerve-sparing radical prostatectomy. The fourth study investigated the onset of action of avanafil at two doses (100 and 200 mg) in terms of per-subject proportion of sexual attempts resulting in satisfactory completion of sexual intercourse. A total of 1774 patients received avanafil, which was taken as needed at doses of 50 mg (one study), 100 mg and 200 mg (four studies), respectively. Patients were instructed to take 1 dose of study medicinal product approximately 30 minutes prior to initiation of sexual activity. In the fourth study patients were encouraged to attempt sexual intercourse approximately 15 minutes post-dosing, to assess the onset of the erectogenic effect of avanafil, taken on an as needed basis, at 100 and 200 mg dose.

In addition, a subset of patients was enrolled into an open-label extension trial with 493 patients receiving avanafil for at least 6 months and 153 patients for at least 12 months. Patients were initially assigned to avanafil 100 mg and at any point during the trial, they could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based on their individual response to treatment.

In all trials, statistically significant improvement in all primary efficacy measures were observed for all three doses of avanafil compared to placebo. These differences were maintained with long term treatment (as per studies in the general ED population, in diabetics with ED and in men with ED following bilateral nerve-sparing radical prostatectomy and in the open-label extension trial).

In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo.

In men with either Type 1 or Type 2 diabetes mellitus, the mean percentage of attempts resulting in successful intercourse was approximately 34% and 40% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 21% for the placebo group.

In men with ED following bilateral nerve-sparing radical prostatectomy, the mean percentage of attempts resulting in successful intercourse was approximately 23% and 26% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 9% for placebo.

In the Time to onset study, avanafil demonstrated statistically significant improvement in the primary efficacy variable (average per subject proportion of successful responses by time after dose administration, to the Sexual Encounter Profile 3 – SEP3) as compared with placebo, resulting in successful intercourse in 24.71% of the attempts for the 100 mg dose and 28.18% for the 200 mg dose at approximately 15 minutes after dosing compared to 13.78% for placebo.

Across all of the pivotal trials of avanafil, the percentage of successful intercourse attempts was significantly higher for all doses of avanafil compared to placebo for attempts at all post-dosing time intervals examined.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Spedra in all subsets of the paediatric population in erectile dysfunction (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4). The concomitant use of potent CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) is associated with increased plasma exposure of avanafil (see section 4.5). Avanafil has a terminal half-life of approximately 6-17 hours.

Absorption

Avanafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 0.5 to 0.75 hours of oral dosing in the fasted state. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There was no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance.

Distribution

Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total active substance concentrations, age, renal and hepatic function. Avanafil was not found to accumulate in plasma when dosed 200 mg twice daily over 7 days. Based upon measurements of avanafil in semen of healthy volunteers 45-90 minutes after dosing, less than 0.0002% of the administered dose may appear in the semen of patients.

Biotransformation

Avanafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite shows a phosphodiesterase selectivity profile similar to that of avanafil and an *in vitro* inhibitory potency for PDE5 18% of that of avanafil. Therefore, M4 accounts for approximately 4% of total pharmacologic activity. The M16 metabolite was inactive against PDE5.

Elimination

Avanafil is extensively metabolised in humans. After oral administration, avanafil is excreted as metabolites predominantly in the faeces (approximately 63% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose).

Other special populations

Elderly

Older patients (65 years or over) had comparable exposure to that seen in younger patients (18-45 years). However, data on subjects older than 70 years are limited.

Renal impairment

In subjects with mild (creatinine clearance ≥ 50 - < 80 mL/min) and moderate (creatinine clearance ≥ 30 - < 50 mL/min) renal impairment, the pharmacokinetics of a single 200 mg dose of avanafil were not altered. There are no data available for subjects with severe renal insufficiency or end-stage renal disease on haemodialysis.

Hepatic impairment

Subjects with mild hepatic impairment (Child-Pugh A) had comparable exposure to subjects with normal hepatic function when a single dose of 200 mg avanafil was administered.

The exposure 4 hours post-dose was lower in subjects with moderate hepatic impairment (Child-Pugh B) compared to subject with normal hepatic function after 200 mg of avanafil. The maximum concentration and exposure was similar to that observed after subjects with normal hepatic function received an efficacious avanafil 100 mg dose.

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.

In a rat fertility and early embryonic development trial, a decrease in fertility and sperm motility, altered estrous cycles, and an increased percentage of abnormal sperm occurred at 1000 mg/kg/day, a dose which also caused parental toxicity in the treated males and females. No effects on fertility or sperm parameters were noted at doses up to 300 mg/kg/day (in male rats 9 times human exposure based on unbound AUC at a dose of 200 mg). There were no treatment-related testicular findings in mice or rats treated with doses up to 600 or 1000 mg/kg/day for 2 years, and no testicular findings in dogs treated with avanafil for 9 months at exposures 110 times human exposure at the Maximum Recommended Human Dose (MRHD).

In pregnant rats, no evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed at doses up to 300 mg/kg/day (approximately 15 times the MRHD on a mg/m² basis in a 60 kg subject). At a maternally toxic dose of 1000 mg/kg/day (approximately 49 times the MRHD on a mg/m² basis), decreased fetal body weight occurred with no signs of teratogenicity. In pregnant rabbits, no teratogenicity, embryotoxicity or fetotoxicity was observed at doses up to 240 mg/kg/day (approximately 23 times the MRHD on a mg/m² basis). In the rabbit study, maternal toxicity was observed at 240 mg/kg/day.

In a rat pre- and post-natal development study, pups exhibited persistent decreases in body weight at 300 mg/kg/day and higher (approximately 15 times the MRHD on a mg/m² basis) and delayed sexual development at 600 mg/kg/day (approximately 29 times the MRHD on a mg/m² basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Fumaric acid
Hydroxypropylcellulose
Hydroxypropylcellulose, low substituted
Calcium carbonate
Magnesium stearate
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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/PCTFE/Aluminium or PVC/PVDC/Aluminium perforated unit dose blisters in cartons of 2x1, 4x1, 8x1 and 12x1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/004-007
EU/1/13/841/015-018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 2013
Date of latest renewal: 23 April 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Spedra 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of avanafil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Pale yellow oval tablets, debossed with “200” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of erectile dysfunction in adult men.

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

4.2 Posology and method of administration

Posology

Use in adult men

The recommended dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity (see section 5.1). Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.

Special populations

Elderly (≥ 65 years old)

Dose adjustments are not required in elder patients. Limited data are available in elder patients aged 70 years or above.

Renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min). Spedra is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 4.3 and 5.2). Patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min but < 80 mL/min) who were enrolled in phase 3 studies showed decreased efficacy compared to those with normal renal function.

Hepatic impairment

Spedra is contraindicated in patients with severe hepatic impairment (Child Pugh class C) (see sections 4.3 and 5.2). Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum efficacious dose and adjust posology based on tolerance.

Use in men with diabetes

Dose adjustments are not required in diabetic patients.

Paediatric population

There is no relevant use of Spedra in the paediatric population in the indication of erectile dysfunction.

Use in patients using other medicinal products

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is contraindicated (see sections 4.3, 4.4 and 4.5).

In patients receiving concomitant treatment with moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of avanafil should not exceed 100 mg, with an interval of at least 48 hours between doses (see section 4.5).

Method of administration

For oral use. If Spedra is taken with food, the onset of activity may be delayed compared to the fasted state (see section 5.2).

4.3 Contraindications

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

Patients who are using any form of organic nitrate or nitric oxide donors (such as amyl nitrite) (see section 4.5).

The co-administration of type 5 phosphodiesterase (PDE5) inhibitors, including avanafil, with guanylate cyclase stimulators, such as riociguat is contraindicated as it may potentially lead to symptomatic hypotension (see section 4.5).

Physicians should consider the potential cardiac risk of sexual activity in patients with pre-existing cardiovascular disease before prescribing Spedra.

The use of avanafil is contraindicated in:

- Patients who have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg);
- Patients with unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater.

Patients with severe hepatic impairment (Child-Pugh C).

Patients with severe renal impairment (creatinine clearance < 30 mL/min).

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).

Patients with known hereditary degenerative retinal disorders.

Patients who are using potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) (see sections 4.2, 4.4 and 4.5).

4.4 Special warnings and precautions for use

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

Cardiovascular status

Prior to initiating any treatment for erectile dysfunction, physicians should consider the cardiovascular status of their patients since there is a degree of cardiac risk associated with sexual activity (see section 4.3). Avanafil has vasodilator properties, resulting in mild and transient decreases in blood pressure (see section 4.5), and as such potentiates the hypotensive effect of nitrates (see section 4.3). Patients with left ventricular outflow obstruction, e.g. aortic stenosis and idiopathic hypertrophic subaortic stenosis, can be sensitive to the action of vasodilators, including PDE5 inhibitors.

Priapism

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

Visual problems

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 PDE5 inhibitors. The patient should be advised that in case of sudden visual effects he should stop taking Spedra and consult a physician immediately (see section 4.3).

Effect on bleeding

In vitro studies with human platelets indicate that PDE5 inhibitors do not have an effect on platelet aggregation on their own, but at supratherapeutic doses they potentiate the anti-aggregatory effect of the nitric oxide donor sodium nitroprusside. In humans, PDE5 inhibitors do not appear to affect bleeding time alone or in combination with acetylsalicylic acid.

There is no safety information on the administration of avanafil to patients with bleeding disorders or active peptic ulceration. Therefore, avanafil should be administered to such patients only after careful benefit-risk assessment.

Decreased or sudden loss of hearing

Patients should be advised to stop taking PDE5 inhibitors, including avanafil, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

Concomitant use of alpha-blockers

The concomitant use of alpha-blockers and avanafil may lead to symptomatic hypotension in some patients due to additive vasodilatory effects (see section 4.5). Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating Spedra. Patients who demonstrate haemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of avanafil.
- In those patients who are stable on alpha-blocker therapy, avanafil should be initiated at the lowest dose of 50 mg.
- In those patients already taking an optimised dose of Spedra, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking avanafil.

- The safety of combined use of avanafil and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medicinal products.

Concomitant use of CYP3A4 inhibitors

Co-administration of avanafil with potent inhibitors of CYP3A4, such as ketoconazole or ritonavir is contraindicated (see sections 4.2, 4.3 and 4.5).

Concomitant use of other treatments for erectile dysfunction

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

Concomitant use of alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension (see section 4.5). Patients should be advised that concurrent use of avanafil and alcohol may increase the likelihood of hypotension, dizziness, or syncope. Physicians should also advise patients on what to do in the event of postural hypotensive symptoms.

Populations not studied

Avanafil has not been evaluated in patients with erectile dysfunction due to spinal cord injury or other neurological disorders and in subjects with severe renal or hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for pharmacodynamic interactions with avanafil

Nitrates

Avanafil was shown to augment the hypotensive effects of nitrates compared to placebo in healthy subjects. This is thought to result from the combined effects of nitrates and avanafil on the nitric oxide/cGMP pathway. Therefore, administration of avanafil to patients who are using any form of organic nitrate or nitric oxide donor (such as amyl nitrite) is contraindicated. In a patient who has taken avanafil within 12 hours, where nitrate administration is deemed medically necessary in a life-threatening situation, the likelihood of a significant and potentially dangerous drop in blood pressure is increased. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate haemodynamic monitoring (see section 4.3).

Medicinal products reducing systemic blood pressure

As a vasodilator, avanafil may reduce systemic blood pressure. If Spedra is used in combination with another medicinal product which reduces systemic blood pressure, the additive effects may result in symptomatic hypotension (e.g. dizziness, light-headedness, syncope or near-syncope). In phase III clinical trials no events of “hypotension” but occasional episodes of “dizziness” were observed (see section 4.8). One episode of “syncope” was observed in placebo and one episode on 100 mg of avanafil in phase III clinical trials.

Patients with left ventricular outflow obstruction (e.g. aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the actions of vasodilators including avanafil (see section 4.4).

Alpha-blockers

Haemodynamic interactions with doxazosin and tamsulosin were studied in healthy subjects in a two-period crossover-design trial. In patients receiving stable doxazosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 2.5 mmHg and 6.0 mmHg, respectively. In total, 7/24 subjects experienced values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

In patients receiving stable tamsulosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following avanafil dosing were 3.6 mmHg and 3.1 mmHg,

respectively and 5/24 subjects experienced blood pressure values or decreases from baseline that were of potential clinical significance following avanafil dosing (see section 4.4).

Antihypertensives other than alpha-blockers

A clinical study was conducted to assess the effect of avanafil on the potentiation of the blood pressure-lowering effects of selected antihypertensive medicinal products (amlodipine and enalapril). Results showed a mean maximum decrease in supine blood pressure of 2/3 mmHg compared to placebo with enalapril and 1/-1 mmHg with amlodipine when avanafil was co-administered. There was a statistically significant difference in maximum decrease from baseline in supine diastolic blood pressure with enalapril and avanafil only, which returned to baseline 4 hours after the dose of avanafil. In both cohorts, one subject experienced a decrease in blood pressure without symptoms of hypotension, which resolved within 1 hour of onset. Avanafil had no effect on the pharmacokinetics of amlodipine, but amlodipine increased the maximum and total exposure of avanafil by 28% and 60%, respectively (see section 4.4).

Alcohol

Consumption of alcohol in combination with avanafil can increase the potential for symptomatic hypotension. In a single-dose three-way crossover design study evaluating healthy subjects, the mean maximum reduction in diastolic blood pressure was significantly greater following avanafil administered in combination with alcohol than following avanafil alone (3.2 mmHg) or alcohol alone (5.0 mmHg) (see section 4.4).

Other treatments for erectile dysfunction

The safety and efficacy of combinations of avanafil and other PDE5 inhibitors or other treatments for erectile dysfunction have not been studied (see section 4.4).

Effects of other substances on avanafil

Avanafil is a substrate of and predominantly metabolised by CYP3A4. Studies have shown that medicinal products that inhibit CYP3A4 can increase avanafil exposure (see section 4.2).

CYP3A4 Inhibitors

Ketoconazole (400 mg daily), a selective and highly potent inhibitor of CYP3A4, increased avanafil 50 mg single-dose C_{max} and exposure (AUC) equal to 3-fold and 14-fold respectively and prolonged the half-life of avanafil to approximately 9 hours. Ritonavir (600 mg twice daily), a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9, increased avanafil 50 mg single-dose C_{max} and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of avanafil to approximately 9 hours. Other strong inhibitors of CYP3A4 (e.g. itraconazole, voriconazole, clarithromycin, nefazodone, saquinavir, nelfinavir, indinavir, atazanavir, and telithromycin) would be expected to have similar effects. Consequently, co-administration of avanafil with potent CYP3A4 inhibitors is contraindicated (see sections 4.2, 4.3 and 4.4).

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, increased avanafil 200 mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of avanafil to approximately 8 hours. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil) would be expected to have similar effects. Consequently, the maximum recommended dose of avanafil is 100 mg, not to exceed once every 48 hours for patients taking concomitant moderate CYP3A4 inhibitors (see section 4.2).

Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice would likely increase avanafil exposure. Patients should be advised to avoid grapefruit juice within 24 hours prior to taking avanafil.

CYP3A4 substrate

Amlodipine (5 mg daily) increased avanafil 200 mg single-dose C_{max} and AUC by approximately 28% and 60%, respectively. These exposure changes are not considered clinically significant. There was no effect of a single dose of avanafil on amlodipine plasma levels.

Although specific interactions of avanafil with rivaroxaban and apixaban (both CYP3A4 substrates) have not been studied, an interaction is not expected.

Cytochrome P450 Inducers

The potential effect of CYP inducers, especially inducers of CYP3A4 (e.g. bosentan, carbamazepine, efavirenz, phenobarbital and rifampicin) on the pharmacokinetics and efficacy of avanafil has not been evaluated. The concomitant use of avanafil and a CYP inducer is not recommended as it may decrease the efficacy of avanafil.

Effects of avanafil on other medicinal products

Cytochrome P450 Inhibition

In *in vitro* studies in human liver microsomes, avanafil showed a negligible potential for drug-drug interactions with CYP1A1/2, 2A6, 2B6 and 2E1. Further, the metabolites of avanafil (M4, M16 and M27), also demonstrated a minimal inhibition of CYPs 1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Based on these data avanafil is not anticipated to have a significant effect on other medicinal products metabolised by these enzymes.

Since the *in vitro* data identified potential avanafil interactions with CYPs 2C19, 2C8/9, 2D6 and 3A4, further clinical studies using omeprazole, rosiglitazone and desipramine did not reveal clinically relevant interactions with CYPs 2C19, 2C8/9 and 2D6.

Cytochrome P450 Induction

The potential induction of CYP1A2, CYP2B6 and CYP3A4 by avanafil evaluated in primary human hepatocytes *in vitro* did not reveal any potential interaction at clinically relevant concentrations.

Transporters

In vitro results showed for avanafil a modest potential for acting as P-gp substrate and P-gp inhibitor with digoxin as a substrate at concentrations lower than the calculated intestinal concentration. The potential of avanafil to interfere with the transport of other medicinal products mediated by P-gp is not known.

Based on *in vitro* data, at clinically relevant concentrations avanafil could be an inhibitor of BCRP. At clinically relevant concentrations avanafil is not an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 and BSEP.

The impact of avanafil on other transporters is unknown.

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effect when PDE 5 inhibitors were combined with riociguat. In clinical studies, riociguat has 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 avanafil, is contraindicated (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy

Spedra is not indicated for use in women.

There are no data from the use of avanafil 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).

Breast-feeding

There are no data on the use of avanafil during breast-feeding.

Fertility

There was no effect on sperm motility or morphology after single 200 mg oral doses of avanafil in healthy volunteers.

In a clinical trial performed in healthy volunteers and adult males with mild erectile dysfunction, the daily administration of avanafil 100 mg oral doses over a period of 26 weeks was not associated with any untoward effects on sperm concentration, count, motility, or morphology .

4.7 Effects on ability to drive and use machines

Spedra has minor influence on the ability to drive and use machines. As dizziness and altered vision were reported in clinical trials with avanafil, patients should be aware of how they react to Spedra before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of Spedra is based on 2,566 subjects exposed to avanafil during the clinical development program. The most common adverse reactions reported in clinical studies were headache, flushing, nasal and sinus congestion and back pain. Overall adverse events and adverse reactions for avanafil-treated subjects were more frequent in subjects with a Body Mass Index (BMI) <25 (normal BMI subjects).

In the long term clinical study, the percentage of patients who experienced adverse reactions decreased with increasing length of exposure.

Tabulated list of adverse reactions

The table below lists the adverse reactions observed in placebo-controlled clinical trials according to the MedDRA 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 available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Infections and infestations			Influenza Nasopharyngitis
Immune system disorders			Seasonal allergy
Metabolism and nutrition disorders			Gout
Psychiatric disorders			Insomnia Premature ejaculation Inappropriate affect
Nervous system disorders	Headache	Dizziness Somnolence Sinus headache	Psychomotor hyperactivity
Eye disorders		Vision blurred	
Cardiac disorders		Palpitations	Angina pectoris Tachycardia
Vascular disorders	Flushing	Hot flush	Hypertension
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Sinus congestion Dyspnoea exertional	Rhinorrhoea Upper respiratory tract congestion Epistaxis

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	Common	Uncommon	Rare
Gastrointestinal disorders		Dyspepsia Nausea Vomiting Stomach discomfort	Dry mouth Gastritis Abdominal pain lower Diarrhoea
Skin and subcutaneous tissue disorders			Rash
Musculoskeletal and connective tissue disorders		Back pain Muscle tightness	Flank pain Myalgia Muscle spasms
Renal and urinary disorders			Pollakiuria
Reproductive system and breast disorders			Penis disorder Spontaneous penile erection Pruritus genital
General disorders and administration site conditions		Fatigue	Asthenia Chest pain Influenza like illness Oedema peripheral
Investigations		Hepatic enzyme increased Electrocardiogram abnormal Heart rate increased	Blood pressure increased Blood urine present Cardiac murmur Prostate specific antigen increased Weight increased Blood bilirubin increased Blood creatinine increased Body temperature increased

Description of selected adverse reactions observed with other PDE5 inhibitors

Non-arteritic anterior ischaemic optic neuropathy (NAION) and sudden loss of hearing have been reported in a small number of postmarketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil (see section 4.4).

Priapism has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors. No cases were reported during clinical trials of avanafil.

Haematuria, haemospermia and penile haemorrhage has been reported in a small number of post-marketing and clinical trial cases with other PDE5 inhibitors.

Hypotension has been reported post marketing with other PDE5 inhibitors, and dizziness, a symptom commonly caused by lowered blood pressure, has been reported in clinical trials with avanafil (see section 4.5).

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](#).

4.9 Overdose

Single dose of up to 800 mg of avanafil have been given to healthy subjects and multiple daily doses up to 300 mg have been given to patients. Adverse reactions were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as avanafil is highly bound to plasma proteins and it is not eliminated in the urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals: Drugs used in erectile dysfunction.
ATC code: G04BE10.

Mechanism of action

Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5. When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by avanafil produces increased levels of cGMP in the corpus cavernosum of the penis. This results in smooth muscle relaxation and inflow of blood into the penile tissues, thereby producing an erection. Avanafil has no effect in the absence of sexual stimulation.

Pharmacodynamic effects

Studies *in vitro* have shown that avanafil is highly selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (> 100-fold for PDE6; > 1,000-fold for PDE4, PDE8 and PDE10; > 5,000-fold for PDE2 and PDE7; > 10,000-fold for PDE1, PDE3, PDE9, and PDE11). Avanafil is > 100-fold more potent for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction. The approximately 20,000-fold selectivity for PDE5 versus PDE3, and enzyme found in heart and blood vessels, is important because PDE3 is involved in control of cardiac contractility.

In a penile plethysmography (RigiScan) study, avanafil 200 mg produced erections considered sufficient for penetration (60% rigidity by RigiScan) in some men as early as 20 minutes after dosing and overall response of these subjects to avanafil was statistically significant, compared to placebo, in the 20-40 minute time interval.

Clinical efficacy and safety

In clinical trials, avanafil was assessed for its effect on the ability of men with erectile dysfunction (ED) to achieve and maintain an erection sufficient for satisfactory sexual activity. Avanafil was evaluated in 4 randomized, double-blind, placebo-controlled, parallel group trials of up to 3 months in duration in the general population with ED, in patients with Type 1 or Type 2 diabetes and ED, and in patients with ED following bilateral nerve-sparing radical prostatectomy. The fourth study investigated the onset of action of avanafil at two doses (100 and 200 mg) in terms of per-subject proportion of sexual attempts resulting in satisfactory completion of sexual intercourse. A total of 1774 patients received avanafil, which was taken as needed at doses of 50 mg (one study), 100 mg and 200 mg (four studies), respectively. Patients were instructed to take 1 dose of study medicinal product approximately 30 minutes prior to initiation of sexual activity. In the fourth study patients were encouraged to attempt sexual intercourse approximately 15 minutes post-dosing, to assess the onset of the erectogenic effect of avanafil, taken on an as needed basis, at 100 and 200 mg dose.

In addition, a subset of patients was enrolled into an open-label extension trial with 493 patients receiving avanafil for at least 6 months and 153 patients for at least 12 months. Patients were initially

assigned to avanafil 100 mg and at any point during the trial, they could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based on their individual response to treatment.

In all trials, statistically significant improvement in all primary efficacy measures were observed for all three doses of avanafil compared to placebo. These differences were maintained with long term treatment (as per studies in the general ED population, in diabetics with ED and in men with ED following bilateral nerve-sparing radical prostatectomy and in the open-label extension trial).

In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo.

In men with either Type 1 or Type 2 diabetes mellitus, the mean percentage of attempts resulting in successful intercourse was approximately 34% and 40% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 21% for the placebo group.

In men with ED following bilateral nerve-sparing radical prostatectomy, the mean percentage of attempts resulting in successful intercourse was approximately 23% and 26% for the 100 mg and 200 mg avanafil groups, respectively, compared to approximately 9% for placebo.

In the Time to onset study, avanafil demonstrated statistically significant improvement in the primary efficacy variable (average per subject proportion of successful responses by time after dose administration, to the Sexual Encounter Profile 3 – SEP3) as compared with placebo, resulting in successful intercourse in 24.71% of the attempts for the 100 mg dose and 28.18% for the 200 mg dose at approximately 15 minutes after dosing compared to 13.78% for placebo.

Across all of the pivotal trials of avanafil, the percentage of successful intercourse attempts was significantly higher for all doses of avanafil compared to placebo for attempts at all post-dosing time intervals examined.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Spedra in all subsets of the paediatric population in erectile dysfunction (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly CYP3A4). The concomitant use of potent CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) is associated with increased plasma exposure of avanafil (see section 4.5). Avanafil has a terminal half-life of approximately 6-17 hours.

Absorption

Avanafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 0.5 to 0.75 hours of oral dosing in the fasted state. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There was no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance.

Distribution

Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total active substance concentrations, age, renal and hepatic function. Avanafil was not found to accumulate in plasma when dosed 200 mg twice daily over 7 days. Based upon measurements of avanafil in semen of healthy volunteers 45-90 minutes after dosing, less than 0.0002% of the administered dose may appear in the semen of patients.

Biotransformation

Avanafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite shows a phosphodiesterase selectivity profile similar to that of avanafil and an *in vitro* inhibitory potency for PDE5 18% of that of avanafil. Therefore, M4 accounts for approximately 4% of total pharmacologic activity. The M16 metabolite was inactive against PDE5.

Elimination

Avanafil is extensively metabolised in humans. After oral administration, avanafil is excreted as metabolites predominantly in the faeces (approximately 63% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose).

Other special populations

Elderly

Older patients (65 years or over) had comparable exposure to that seen in younger patients (18-45 years). However, data on subjects older than 70 years are limited.

Renal impairment

In subjects with mild (creatinine clearance ≥ 50 - < 80 mL/min) and moderate (creatinine clearance ≥ 30 - < 50 mL/min) renal impairment, the pharmacokinetics of a single 200 mg dose of avanafil were not altered. There are no data available for subjects with severe renal insufficiency or end-stage renal disease on haemodialysis.

Hepatic impairment

Subjects with mild hepatic impairment (Child-Pugh A) had comparable exposure to subjects with normal hepatic function when a single dose of 200 mg avanafil was administered.

The exposure 4 hours post-dose was lower in subjects with moderate hepatic impairment (Child-Pugh B) compared to subject with normal hepatic function after 200 mg of avanafil. The maximum concentration and exposure was similar to that observed after subjects with normal hepatic function received an efficacious avanafil 100 mg dose.

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.

In a rat fertility and early embryonic development trial, a decrease in fertility and sperm motility, altered estrous cycles, and an increased percentage of abnormal sperm occurred at 1000 mg/kg/day, a dose which also caused parental toxicity in the treated males and females. No effects on fertility or sperm parameters were noted at doses up to 300 mg/kg/day (in male rats 9 times human exposure based on unbound AUC at a dose of 200 mg). There were no treatment-related testicular findings in mice or rats treated with doses up to 600 or 1000 mg/kg/day for 2 years, and no testicular findings in dogs treated with avanafil for 9 months at exposures 110 times human exposure at the Maximum Recommended Human Dose (MRHD).

In pregnant rats, no evidence of teratogenicity, embryotoxicity, or fetotoxicity was observed at doses up to 300 mg/kg/day (approximately 15 times the MRHD on a mg/m² basis in a 60 kg subject). At a maternally toxic dose of 1000 mg/kg/day (approximately 49 times the MRHD on a mg/m² basis), decreased fetal body weight occurred with no signs of teratogenicity. In pregnant rabbits, no teratogenicity, embryotoxicity or fetotoxicity was observed at doses up to 240 mg/kg/day (approximately 23 times the MRHD on a mg/m² basis). In the rabbit study, maternal toxicity was observed at 240 mg/kg/day.

In a rat pre- and post-natal development study, pups exhibited persistent decreases in body weight at 300 mg/kg/day and higher (approximately 15 times the MRHD on a mg/m² basis) and delayed sexual development at 600 mg/kg/day (approximately 29 times the MRHD on a mg/m² basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Fumaric acid
Hydroxypropylcellulose
Hydroxypropylcellulose, low substituted
Calcium carbonate
Magnesium stearate
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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/PCTFE/Aluminium or PVC/PVDC/Aluminium perforated unit dose blisters in cartons of 2x1, 4x1, 8x1 and 12x1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/008-011
EU/1/13/841/019-022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 June 2013

Date of the latest renewal: 23 April 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Menarini - Von Heyden GmbH
Leipziger Straße 7-13
01097 Dresden
Germany

or

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambares et Lagrave
33565 Carbon-Blanc-Cedex
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spedra 50 mg tablets
avanafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg avanafil.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4x1 tablets
8x1 tablets
12x1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/001 4x1 tablets
EU/1/13/841/002 8x1 tablets
EU/1/13/841/003 12x1 tablets
EU/1/13/841/012 4x1 tablets
EU/1/13/841/013 8x1 tablets
EU/1/13/841/014 12x1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spedra 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Spedra 50 mg tablets
avanafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini Luxembourg

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spedra 100 mg tablets
avanafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg avanafil.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2x1 tablets
4x1 tablets
8x1 tablets
12x1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/004 2x1 tablets
EU/1/13/841/005 4x1 tablets
EU/1/13/841/006 8x1 tablets
EU/1/13/841/007 12x1 tablets
EU/1/13/841/015 2x1 tablets
EU/1/13/841/016 4x1 tablets
EU/1/13/841/017 8x1 tablets
EU/1/13/841/018 12x1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spedra 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Spedra 100 mg tablets
avanafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini Luxembourg

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spedra 200 mg tablets
avanafil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg avanafil.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4x1 tablets
8x1 tablets
12x1 tablets
2x1 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.
1, Avenue de la Gare, L-1611 Luxembourg
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/841/008 4x1 tablets
EU/1/13/841/009 8x1 tablets
EU/1/13/841/010 12x1 tablets
EU/1/13/841/011 2x1 tablets
EU/1/13/841/019 2x1 tablets
EU/1/13/841/020 4x1 tablets
EU/1/13/841/021 8x1 tablets
EU/1/13/841/022 12x1 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spedra 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Spedra 200 mg tablets
avanafil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Menarini Luxembourg

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Spedra 50 mg tablets avanafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spedra is and what it is used for
2. What you need to know before you take Spedra
3. How to take Spedra
4. Possible side effects
5. How to store Spedra
6. Contents of the pack and other information

1. What Spedra is and what it is used for

Spedra contains the active substance avanafil. It belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. Spedra is a treatment for adult men suffering from erectile dysfunction (also known as impotence). This is when you cannot get, or keep a hard, erect penis suitable for sexual activity.

Spedra works by helping the blood vessels in your penis to relax. This increases the blood flow into your penis, helping it stay hard and erect when you get sexually excited. Spedra does not cure your condition.

It is important to note that Spedra only works if you are sexually stimulated. You and your partner will still need to use foreplay to get ready for sex – just as you would if you were not taking a medicine to help you.

Spedra will not help you if you do not have erectile dysfunction. Spedra is not for women.

2. What you need to know before you take Spedra

Do not take Spedra:

- If you are allergic to avanafil or any of the other ingredients of this medicine (listed in section 6)
- If you are taking “nitrate” medicines for chest pain (angina), such as amyl nitrite or glyceryl trinitrate. Spedra can increase the effects of these medicines and severely lower your blood pressure
- If you are taking s for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir
- If you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or certain antibiotics for bacterial infections, such as clarithromycin or telithromycin

- If you have a serious cardiac problem
- If you have had a stroke or heart attack in the last 6 months
- If you have low blood pressure or high blood pressure not controlled by medicines
- If you have chest pain (angina) or you get chest pain during sexual intercourse
- If you have a serious liver or kidney problem
- If you have loss of vision in one eye due to not enough blood getting to your eye (non-arteritic ischemic optic neuropathy [NAION])
- If certain serious eye problems run in your family (such as retinitis pigmentosa).
- If you are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Do not take Spedra if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Spedra.

Warnings and precautions

Talk to your doctor or pharmacist before taking Spedra:

- If you have heart trouble. It may be risky for you to have sexual intercourse
- If you suffer from priapism, that is a persistent erection lasting 4 hours or more. This can happen in men with conditions like sickle cell disease, multiple myeloma or leukaemia.
- If you have a physical condition that affects the shape of your penis (such as angulation, Peyronie's disease or cavernosal fibrosis)
- If you have any bleeding disorder or active peptic ulceration.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Problems with your sight or hearing

Some men taking medicines like Spedra have had problems with their sight and hearing – see “Serious side effects” in section 4 for more details. It is not known if these problems are related directly to Spedra, other diseases that you may have or a combination of factors.

If you experience sudden decrease or loss of vision or your vision is distorted or dimmed while you are taking Spedra, stop taking Spedra and contact your doctor immediately.

Children and adolescents

Spedra should not be taken by children and adolescents under 18 years of age.

Other medicines and Spedra

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Spedra can affect the way some other medicines work. Also some other medicines can affect the way Spedra works.

In particular, tell your doctor and do not take Spedra if you are taking “nitrate” medicines for chest pain (angina) such as amyl nitrite or glyceryl trinitrate. Spedra has been shown to increase the effects of these medicines and severely lower your blood pressure. Also do not take Spedra if you are taking medicines for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir or if you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or certain antibiotics for bacterial infections, such as clarithromycin or telithromycin (see beginning of section 2 under ‘Do not take Spedra’).

Tell your doctor or pharmacist if you are taking any of the following medicines:

- so called “alpha-blockers” – for prostate problems or for lowering your high blood pressure
- medicines for an irregular heartbeat (“arrhythmia”) such as quinidine, procainamide, amiodarone or sotalol
- antibiotics for infections such as erythromycin
- phenobarbital or primidone – for epilepsy
- carbamazepine – for epilepsy, to stabilise your mood or for certain types of pain
- other medicines that may reduce the breakdown of Spedra in the body (‘moderate CYP3A4 inhibitors’) including amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil.
- riociguat

Do not use Spedra together with other treatments for erectile dysfunction such as sildenafil, tadalafil or vardenafil.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Spedra with drink and alcohol

Grapefruit juice can increase exposure to the medicine and should be avoided within 24 hours prior to taking Spedra.

Drinking alcohol at the same time as taking Spedra may increase your heart rate and lower your blood pressure. You may feel dizzy (especially when standing), have a headache or feel your heart beating in your chest (palpitations). Drinking alcohol may also decrease your ability to get an erection.

Fertility

There was no effect on sperm movement or structure after single 200 mg oral doses of avanafil in healthy volunteers.

The repeated oral administration of avanafil 100 mg over a period of 26 weeks to healthy volunteers and adult males with mild erectile dysfunction was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

Driving and using machines

Spedra can make you feel dizzy or affect your vision. If this happens, do not drive, cycle, use tools or machines.

3. How to take Spedra

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is a 100 mg tablet, as needed. You should not take Spedra more than once a day. You could have been given the dose of one 200 mg tablet if your doctor has decided that the 100 mg dose was too weak for you, or the dose of one 50 mg tablet if your doctor has decided that the 100 mg tablet was too strong for you. Dose adjustments can also be required if Spedra is used together with certain other medicines. If you are taking a medicine such as erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir or verapamil (‘moderate CYP3A4 inhibitors’) the recommended dose of Spedra is a 100 mg tablet, with an interval of at least 2 days between doses. You should take Spedra about 30 minutes before you have sexual intercourse. Remember that Spedra will only help you to get an erection if you are sexually stimulated.

Spedra can be taken with or without food; if taken with food, it may take longer to work.

If you take more Spedra than you should

If you take too much Spedra, you should tell your doctor straight away. You may get more side effects than usual and they may be worse.

If you have any further questions on the use of Spedra, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop taking Spedra and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- an erection that will not go away (“priapism”). If you get an erection that lasts more than 4 hours, this must be treated as soon as possible or lasting damage can happen to your penis (including not being able to get erections).
- blurred vision.
- sudden decrease or loss of vision in one or both eyes.
- sudden decrease or loss of hearing (sometimes you may also feel dizzy or have ringing in your ears).

Stop taking Spedra and see a doctor straight away, if you notice any of the serious side effects above.

Other side effects include:

Common (may affect up to 1 in 10 people)

- headache
- flushing
- nasal congestion

Uncommon (may affect up to 1 in 100 people)

- feeling dizzy
- feeling sleepy or very tired
- sinus congestion
- back pain
- hot flush
- feeling out of breath when you exert yourself
- heartbeat changes seen on a heart tracing (ECG)
- increased heart beat
- feeling your heartbeat in your chest (palpitations)
- indigestion, feeling or being sick to your stomach
- blurry vision
- raised liver enzymes

Rare (may affect up to 1 in 1,000 people)

- influenza
- influenza-like illness
- stuffy or runny nose
- hayfever
- congestion in the nose, sinuses or upper part of the airway bringing air into the lungs
- gout
- trouble sleeping (insomnia)

- premature ejaculation
- feeling strange
- feeling unable to keep still
- chest pain
- serious chest pain
- fast heart beat
- high blood pressure
- dry mouth
- stomach ache or heartburn
- pain or discomfort in the lower abdomen
- diarrhoea
- rash
- pain in the lower back or side of lower chest
- muscle aches or pains
- muscle spasms
- frequent urination
- penile disorder
- spontaneous erection without sexual stimulation
- itching in the genital area
- feeling weak or tired all the time
- swelling in the feet or ankles
- increased blood pressure
- pink or red urine, blood in the urine
- abnormal extra sound from the heart
- an abnormal blood test result for a prostate test called 'PSA'
- an abnormal blood test result for bilirubin, a chemical produced from the normal breakdown of red blood cells
- an abnormal blood test result for creatinine, a chemical excreted in the urine, and a measure of kidney function
- weight gain
- fever
- nosebleed

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spedra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage condition.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spedra contains

- The active substance is avanafil. Each tablet contains 50 mg of avanafil.
- The other ingredients are mannitol, fumaric acid, hydroxypropylcellulose, hydroxypropylcellulose low substituted, calcium carbonate, magnesium stearate and ferric oxide yellow (E172).

What Spedra looks like and contents of the pack

Spedra is a pale yellow oval tablet, marked “50” on one side. The tablets are provided in perforated unit dose blister packs containing 4x1, 8x1, or 12x1 tablets.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder:

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.,
1, Avenue de la Gare,
L-1611 Luxembourg,
Luxembourg.

Manufacturer:

Menarini - Von Heyden GmbH
Leipziger Straße 7-13
01097 Dresden
Germany

or

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambares et Lagrave
33565 Carbon-Blanc-Cedex
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Sverige

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

**Package leaflet: Information for the patient
Spedra 100 mg tablets**

avanafil

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spedra is and what it is used for
2. What you need to know before you take Spedra
3. How to take Spedra
4. Possible side effects
5. How to store Spedra
6. Contents of the pack and other information

1. What Spedra is and what it is used for

Spedra contains the active substance avanafil. It belongs to a group of medicines called phosphodiesterase type 5 (PDE5) inhibitors. Spedra is a treatment for adult men suffering from erectile dysfunction (also known as impotence). This is when you cannot get, or keep a hard, erect penis suitable for sexual activity.

Spedra works by helping the blood vessels in your penis to relax. This increases the blood flow into your penis, helping it stay hard and erect when you get sexually excited. Spedra does not cure your condition.

It is important to note that Spedra only works if you are sexually stimulated. You and your partner will still need to use foreplay to get ready for sex – just as you would if you were not taking a medicine to help you.

Spedra will not help you if you do not have erectile dysfunction. Spedra is not for women.

2. What you need to know before you take Spedra

Do not take Spedra:

- If you are allergic to avanafil or any of the other ingredients of this medicine (listed in section 6)
- If you are taking “nitrate” medicines for chest pain (angina), such as amyl nitrite or glyceryl trinitrate. Spedra can increase the effects of these medicines and severely lower your blood pressure
- If you are taking medicines for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir

- If you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or certain antibiotics for bacterial infections, such as clarithromycin or telithromycin
- If you have a serious cardiac problem
- If you have had a stroke or heart attack in the last 6 months
- If you have low blood pressure or high blood pressure not controlled by medicines
- If you have chest pain (angina) or you get chest pain during sexual intercourse
- If you have a serious liver or kidney problem
- If you have loss of vision in one eye due to not enough blood getting to your eye (non-arteritic ischemic optic neuropathy [NAION])
- If certain serious eye problems run in your family (such as retinitis pigmentosa).
- If you are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Do not take Spedra if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Spedra.

Warnings and precautions

Talk to your doctor or pharmacist before taking Spedra:

- If you have heart trouble. It may be risky for you to have sexual intercourse
- If you suffer from priapism, that is a persistent erection lasting 4 hours or more. This can happen in men with conditions like sickle cell disease, multiple myeloma or leukaemia.
- If you have a physical condition that affects the shape of your penis (such as angulation, Peyronie’s disease or cavernosal fibrosis)
- If you have any bleeding disorder or active peptic ulceration.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Problems with your sight or hearing

Some men taking medicines like Spedra have had problems with their sight and hearing – see “Serious side effects” in section 4 for more details. It is not known if these problems are related directly to Spedra, other diseases that you may have or a combination of factors.

If you experience sudden decrease or loss of vision or your vision is distorted or dimmed while you are taking Spedra, stop taking Spedra and contact your doctor immediately.

Children and adolescents

Spedra should not be taken by children and adolescents under 18 years of age.

Other medicines and Spedra

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Spedra can affect the way some other medicines work. Also some other medicines can affect the way Spedra works.

In particular, tell your doctor and do not take Spedra if you are taking “nitrate” medicines for chest pain (angina) such as amyl nitrite or glyceryl trinitrate. Spedra has been shown to increase the effects of these medicines and severely lower your blood pressure. Also do not take Spedra if you are taking medicines for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir or if you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or

certain antibiotics for bacterial infections, such as clarithromycin or telithromycin (see beginning of section 2 under ‘Do not take Spedra’).

Tell your doctor or pharmacist if you are taking any of the following medicines:

- so called “alpha-blockers” – for prostate problems or for lowering your high blood pressure
- medicines for an irregular heartbeat (“arrhythmia”) such as quinidine, procainamide, amiodarone or sotalol
- antibiotics for infections such as erythromycin
- phenobarbital or primidone – for epilepsy
- carbamazepine – for epilepsy, to stabilise your mood or for certain types of pain
- other medicines that may reduce the breakdown of Spedra in the body (‘moderate CYP3A4 inhibitors’) including amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil.
- riociguat

Do not use Spedra together with other treatments for erectile dysfunction such as sildenafil, tadalafil or vardenafil.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Spedra with drink and alcohol

Grapefruit juice can increase exposure to the medicine and should be avoided within 24 hours prior to taking Spedra.

Drinking alcohol at the same time as taking Spedra may increase your heart rate and lower your blood pressure. You may feel dizzy (especially when standing), have a headache or feel your heart beating in your chest (palpitations). Drinking alcohol may also decrease your ability to get an erection.

Fertility

There was no effect on sperm movement or structure after single 200 mg oral doses of avanafil in healthy volunteers.

The repeated oral administration of avanafil 100 mg over a period of 26 weeks to healthy volunteers and adult males with mild erectile dysfunction was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

Driving and using machines

Spedra can make you feel dizzy or affect your vision. If this happens, do not drive, cycle, use tools or machines.

3. How to take Spedra

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is a 100 mg tablet, as needed. You should not take Spedra more than once a day. You could have been given the dose of one 200 mg tablet if your doctor has decided that the 100 mg dose was too weak for you, or the dose of one 50 mg tablet if your doctor has decided that the 100 mg tablet was too strong for you. Dose adjustments can also be required if Spedra is used together with certain other medicines. If you are taking a medicine such as erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir or verapamil (‘moderate CYP3A4 inhibitors’) the recommended dose of Spedra is a 100 mg tablet, with an interval of at least 2 days between doses.

You should take Spedra approximately 15 to 30 minutes before you have sexual intercourse. Remember that Spedra will only help you to get an erection if you are sexually stimulated. Spedra can be taken with or without food; if taken with food, it may take longer to work.

If you take more Spedra than you should

If you take too much Spedra, you should tell your doctor straight away. You may get more side effects than usual and they may be worse.

If you have any further questions on the use of Spedra, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop taking Spedra and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- an erection that will not go away (“priapism”). If you get an erection that lasts more than 4 hours, this must be treated as soon as possible or lasting damage can happen to your penis (including not being able to get erections).
- blurred vision.
- sudden decrease or loss of vision in one or both eyes.
- sudden decrease or loss of hearing (sometimes you may also feel dizzy or have ringing in your ears).

Stop taking Spedra and see a doctor straight away, if you notice any of the serious side effects above.

Other side effects include:

Common (may affect up to 1 in 10 people)

- headache
- flushing
- nasal congestion

Uncommon (may affect up to 1 in 100 people)

- feeling dizzy
- feeling sleepy or very tired
- sinus congestion
- back pain
- hot flush
- feeling out of breath when you exert yourself
- heartbeat changes seen on a heart tracing (ECG)
- increased heart beat
- feeling your heartbeat in your chest (palpitations)
- indigestion, feeling or being sick to your stomach
- blurry vision
- raised liver enzymes

Rare (may affect up to 1 in 1,000 people)

- influenza
- influenza-like illness
- stuffy or runny nose
- hayfever

- congestion in the nose, sinuses or upper part of the airway bringing air into the lungs
- gout
- trouble sleeping (insomnia)
- premature ejaculation
- feeling strange
- feeling unable to keep still
- chest pain
- serious chest pain
- fast heart beat
- high blood pressure
- dry mouth
- stomach ache or heartburn
- pain or discomfort in the lower abdomen
- diarrhoea
- rash
- pain in the lower back or side of lower chest
- muscle aches or pains
- muscle spasms
- frequent urination
- penile disorder
- spontaneous erection without sexual stimulation
- itching in the genital area
- feeling weak or tired all the time
- swelling in the feet or ankles
- increased blood pressure
- pink or red urine, blood in the urine
- abnormal extra sound from the heart
- an abnormal blood test result for a prostate test called 'PSA'
- an abnormal blood test result for bilirubin, a chemical produced from the normal breakdown of red blood cells
- an abnormal blood test result for creatinine, a chemical excreted in the urine, and a measure of kidney function
- weight gain
- fever
- nosebleed

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spedra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage condition.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spedra contains

- The active substance is avanafil. Each tablet contains 100 mg of avanafil.
- The other ingredients are mannitol, fumaric acid, hydroxypropylcellulose, hydroxypropylcellulose low substituted, calcium carbonate, magnesium stearate and ferric oxide yellow (E172).

What Spedra looks like and contents of the pack

Spedra is a pale yellow oval tablet, marked “100” on one side. The tablets are provided in perforated unit dose blister packs containing 2x1, 4x1, 8x1, or 12x1 tablets.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder:

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.,
1, Avenue de la Gare, L-1611 Luxembourg, Luxembourg

Manufacturer:

Menarini - Von Heyden GmbH
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or

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For any information about this medicine 1 product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

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<http://www.ema.europa.eu>.

Package leaflet: Information for the patient

Spedra 200 mg tablets

avanafil

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What is in this leaflet

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1. What Spedra is and what it is used for

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Spedra works by helping the blood vessels in your penis to relax. This increases the blood flow into your penis, helping it stay hard and erect when you get sexually excited. Spedra does not cure your condition.

It is important to note that Spedra only works if you are sexually stimulated. You and your partner will still need to use foreplay to get ready for sex – just as you would if you were not taking a medicine to help you.

Spedra will not help you if you do not have erectile dysfunction. Spedra is not for women.

2. What you need to know before you take Spedra

Do not take Spedra:

- If you are allergic to avanafil or any of the other ingredients of this medicine (listed in section 6)
- If you are taking “nitrate” medicines for chest pain (angina), such as amyl nitrite or glyceryl trinitrate. Spedra can increase the effects of these medicines and severely lower your blood pressure
- If you are taking medicines for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir

- If you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or certain antibiotics for bacterial infections, such as clarithromycin or telithromycin
- If you have a serious cardiac problem
- If you have had a stroke or heart attack in the last 6 months
- If you have low blood pressure or high blood pressure not controlled by medicines
- If you have chest pain (angina) or you get chest pain during sexual intercourse
- If you have a serious liver or kidney problem
- If you have loss of vision in one eye due to not enough blood getting to your eye (non-arteritic ischemic optic neuropathy [NAION])
- If certain serious eye problems run in your family (such as retinitis pigmentosa).
- If you are taking riociguat. This medicine is used to treat pulmonary arterial hypertension (i.e., high blood pressure in the lungs) and chronic thromboembolic pulmonary hypertension (i.e., high blood pressure in the lungs secondary to blood clots). PDE5 inhibitors have been shown to increase the hypotensive effects of this medicine. If you are taking riociguat or are unsure tell your doctor.

Do not take Spedra if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Spedra.

Warnings and precautions

Talk to your doctor or pharmacist before taking Spedra:

- If you have heart trouble. It may be risky for you to have sexual intercourse
- If you suffer from priapism, that is a persistent erection lasting 4 hours or more. This can happen in men with conditions like sickle cell disease, multiple myeloma or leukaemia.
- If you have a physical condition that affects the shape of your penis (such as angulation, Peyronie's disease or cavernosal fibrosis)
- If you have any bleeding disorder or active peptic ulceration.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Problems with your sight or hearing

Some men taking medicines like Spedra have had problems with their sight and hearing – see “Serious side effects” in section 4 for more details. It is not known if these problems are related directly to Spedra, other diseases that you may have or a combination of factors.

If you experience sudden decrease or loss of vision or your vision is distorted or dimmed while you are taking Spedra, stop taking Spedra and contact your doctor immediately.

Children and adolescents

Spedra should not be taken by children and adolescents under 18 years of age.

Other medicines and Spedra

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Spedra can affect the way some other medicines work. Also some other medicines can affect the way Spedra works.

In particular, tell your doctor and do not take Spedra if you are taking “nitrate” medicines for chest pain (angina) such as amyl nitrite or glyceryl trinitrate. Spedra has been shown to increase the effects of these medicines and severely lower your blood pressure. Also do not take Spedra if you are taking medicines for HIV or AIDS such as ritonavir, indinavir, saquinavir, nelfinavir or atazanavir or if you are taking medicines for fungal infections such as ketoconazole, itraconazole or voriconazole or

certain antibiotics for bacterial infections, such as clarithromycin or telithromycin (see beginning of section 2 under ‘Do not take Spedra’).

Tell your doctor or pharmacist if you are taking any of the following medicines:

- so called “alpha-blockers” – for prostate problems or for lowering your high blood pressure
- medicines for an irregular heartbeat (“arrhythmia”) such as quinidine, procainamide, amiodarone or sotalol
- antibiotics for infections such as erythromycin
- phenobarbital or primidone – for epilepsy
- carbamazepine – for epilepsy, to stabilise your mood or for certain types of pain
- other medicines that may reduce the breakdown of Spedra in the body (‘moderate CYP3A4 inhibitors’) including amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil.
- riociguat

Do not use Spedra together with other treatments for erectile dysfunction such as sildenafil, tadalafil or vardenafil.

If any of the above apply to you talk to your doctor or pharmacist before taking Spedra. Check with your doctor or pharmacist if you are not sure.

Spedra with drink and alcohol

Grapefruit juice can increase exposure to the medicine and should be avoided within 24 hours prior to taking Spedra.

Drinking alcohol at the same time as taking Spedra may increase your heart rate and lower your blood pressure. You may feel dizzy (especially when standing), have a headache or feel your heart beating in your chest (palpitations). Drinking alcohol may also decrease your ability to get an erection.

Fertility

There was no effect on sperm movement or structure after single 200 mg oral doses of avanafil in healthy volunteers.

The repeated oral administration of avanafil 100 mg over a period of 26 weeks to healthy volunteers and adult males with mild erectile dysfunction was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

Driving and using machines

Spedra can make you feel dizzy or affect your vision. If this happens, do not drive, cycle, use tools or machines.

3. How to take Spedra

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The recommended dose is a 100 mg tablet, as needed. You should not take Spedra more than once a day. You could have been given the dose of one 200 mg tablet if your doctor has decided that the 100 mg dose was too weak for you, or the dose of one 50 mg tablet if your doctor has decided that the 100 mg tablet was too strong for you.

Dose adjustments can also be required if Spedra is used together with certain other medicines. If you are taking a medicine such as erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir or verapamil (‘moderate CYP3A4 inhibitors’) the recommended dose of Spedra is a 100 mg tablet, with an interval of at least 2 days between doses.

You should take Spedra approximately 15 to 30 minutes before you have sexual intercourse. Remember that Spedra will only help you to get an erection if you are sexually stimulated. Spedra can be taken with or without food; if taken with food, it may take longer to work.

If you take more Spedra than you should

If you take too much Spedra, you should tell your doctor straight away. You may get more side effects than usual and they may be worse.

If you have any further questions on the use of Spedra, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Stop taking Spedra and see a doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- an erection that will not go away (“priapism”). If you get an erection that lasts more than 4 hours, this must be treated as soon as possible or lasting damage can happen to your penis (including not being able to get erections).
- blurred vision.
- sudden decrease or loss of vision in one or both eyes.
- sudden decrease or loss of hearing (sometimes you may also feel dizzy or have ringing in your ears).

Stop taking Spedra and see a doctor straight away, if you notice any of the serious side effects above.

Other side effects include:

Common (may affect up to 1 in 10 people)

- headache
- flushing
- nasal congestion

Uncommon (may affect up to 1 in 100 people)

- feeling dizzy
- feeling sleepy or very tired
- sinus congestion
- back pain
- hot flush
- feeling out of breath when you exert yourself
- heartbeat changes seen on a heart tracing (ECG)
- increased heart beat
- feeling your heartbeat in your chest (palpitations)
- indigestion, feeling or being sick to your stomach
- blurry vision
- raised liver enzymes

Rare (may affect up to 1 in 1,000 people)

- influenza
- influenza-like illness
- stuffy or runny nose
- hayfever
- congestion in the nose, sinuses or upper part of the airway bringing air into the lungs

- gout
- trouble sleeping (insomnia)
- premature ejaculation
- feeling strange
- feeling unable to keep still
- chest pain
- serious chest pain
- fast heart beat
- high blood pressure
- dry mouth
- stomach ache or heartburn
- pain or discomfort in the lower abdomen
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- frequent urination
- penile disorder
- spontaneous erection without sexual stimulation
- itching in the genital area
- feeling weak or tired all the time
- swelling in the feet or ankles
- increased blood pressure
- pink or red urine, blood in the urine
- abnormal extra sound from the heart
- an abnormal blood test result for a prostate test called 'PSA'
- an abnormal blood test result for bilirubin, a chemical produced from the normal breakdown of red blood cells
- an abnormal blood test result for creatinine, a chemical excreted in the urine, and a measure of kidney function
- weight gain
- fever
- nosebleed

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spedra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage condition.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spedra contains

- The active substance is avanafil. Each tablet contains 200 mg of avanafil.
- The other ingredients are mannitol, fumaric acid, hydroxypropylcellulose, hydroxypropylcellulose low substituted, calcium carbonate, magnesium stearate and ferric oxide yellow (E172).

What Spedra looks like and contents of the pack

Spedra is a pale yellow oval tablet, marked “200” on one side. The tablets are provided in perforated unit dose blister packs containing 2x1, 4x1, 8, or 12x1 tablets.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder:

MENARINI INTERNATIONAL OPERATIONS LUXEMBOURG S.A.,
1, Avenue de la Gare,
L-1611 Luxembourg,
Luxembourg

Manufacturer:

Menarini - Von Heyden GmbH
Leipziger Straße 7-13
01097 Dresden
Germany

or

Sanofi Winthrop Industrie
1, rue de la Vierge
Ambares et Lagrave
33565 Carbon-Blanc-Cedex
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

ANNEX IV
SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for avanafil, the scientific conclusions of PRAC are as follows:

In view of available data on central serous chorioretinopathy from the literature and spontaneous reports including in one case a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between avanafil and central serous chorioretinopathy is at least a reasonable possibility. The PRAC concluded that the product information of products containing avanafil should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for avanafil the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing avanafil is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.