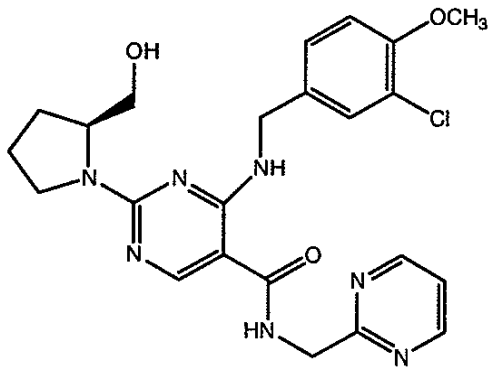
PRODUCT INFORMATION

SPEDRA®

NAME OF THE MEDICINE

avanafil

Chemical Structure



Chemical Name

(*S*)-4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-*N*-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide.

Molecular formula

$C_{23}H_{26}ClN_7O_3$

Molecular weight

484.0

CAS number

330784-47-9

DESCRIPTION

Avanafil is a white crystalline powder. It is slightly soluble in ethanol, practically insoluble in water and soluble in 0.1 mol/L hydrochloric acid.

Avanafil has a partition coefficient of 3.05 (Log P) when measured in 1-Octanol/pH buffer 6.6. The dissociation constants as determined by potentiometric titration are pKa1: <2 and pKa2: 5.2.

SPEDRA tablets are available in strengths of 50mg, 100mg and 200mg tablets. The tablets are pale yellow oval, debossed with the strength (“50”, “100” or “200”) on one side.

SPEDRA tablets contain the following inactive ingredients: mannitol, fumaric acid, hydroxypropylcellulose, calcium carbonate, magnesium stearate and iron oxide yellow.

PHARMACOLOGY

Pharmacodynamics

Avanafil is a reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 by 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.

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 approximate 20,000-fold selectivity for PDE5 versus PDE3, an 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.

Effects on vision

Single oral doses of Type 5 phosphodiesterase inhibitors have demonstrated transient dose-related impairment of colour discrimination (blue/green), using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina.

Avanafil is > 100-fold more potent for PDE5 than PDE6, which is found in the retina and is responsible for phototransduction.

Effects on blood pressure and heart rate

Single oral doses of avanafil (200 mg) administered to healthy male volunteers resulted in mean changes from baseline in systolic/diastolic blood pressure of -5.3/-3.7 mmHg at 1 hour after dosing, compared to mean changes from baseline in the placebo group of 2.7/-0.4 mmHg.

Effects on Cardiac Electrophysiology

The effect of single 100 or 800 mg doses of avanafil on the QT interval were evaluated in a randomised, double-blind, placebo, and active (moxifloxacin)–controlled crossover study in 52 healthy male subjects aged 18 to 45 years. There were no significant effects with the 100 mg dose. The mean QTc (Fridericia QT correction) for avanafil 800 mg, relative to placebo was 9.4 milliseconds (two-sided 90% CI=7.2-11.6). An 800 mg dose of avanafil (4 times the highest recommended dose) was chosen because this dose yields exposures greater than those observed upon co-administration of avanafil with strong CYP3A4 inhibitors. A double-blind, randomised, placebo- and active-controlled (moxifloxacin), thorough QT/QTc trial of avanafil (100 and 800 mg) in healthy male subjects demonstrated that avanafil did not cause any significant changes in QTc interval or ventricular repolarisation.

Effects on Semen

A single 200 mg dose of avanafil had no acute effect on sperm motility or sperm morphology in a group of healthy male subjects. The effect of avanafil on human spermatogenesis is unknown.

Effects on Blood Pressure When Administered with Alcohol

Alcohol and PDE5 inhibitors, including avanafil, are mild systemic vasodilators. The interaction of avanafil with alcohol was evaluated in a clinical pharmacology trial. Alcohol was administered at a dose of 0.5 g/kg, which is equivalent to approximately 88.7 mL of 80-proof vodka in a 70kg male, and avanafil was administered at a dose of 200 mg. All patients consumed the entire alcohol dose within 15 minutes of starting. Blood alcohol levels of 0.057% were confirmed. There were no reports of orthostatic hypotension or dizziness. Additional maximum supine systolic/diastolic blood pressure decreases of 3.5/4.5 mm Hg and additional maximum pulse rate increase of 9.3 BPM were observed when avanafil was taken with alcohol compared to alcohol alone. Avanafil did not affect alcohol plasma concentrations.

Pharmacokinetics

Absorption

Avanafil is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 45 minutes 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% (at the 200 mg dose). The small changes in avanafil C_{max} are considered to be of minimal clinical significance. There was no effect on the extent of exposure (AUC). Patients may need to individualise their dosing relative to their food intake, based on their own experienced clinical response.

The pharmacokinetics of avanafil are dose proportional over the recommended dose range.

Distribution

Avanafil is approximately 99% bound to plasma proteins. Protein binding is independent of total drug substance concentrations, age, renal and hepatic function. Avanafil was not found to accumulate in plasma when administered as 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.

Metabolism

Avanafil is cleared predominantly by hepatic metabolism, mainly by the CYP3A4 enzyme and to a minor extent by the CYP2C isoforms. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% 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 12% of total pharmacologic activity, taking into account relative plasma protein binding. At expected clinical exposures, the M16 metabolite is unlikely to inhibit PDE5.

Excretion

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). Avanafil has a terminal half-life of approximately 6-17 hours.

Pharmacokinetics in Special Populations

Older men: The pharmacokinetics of a single 200 mg avanafil dose administered to fourteen healthy elderly male volunteers (65-80 years) and eighteen healthy younger male volunteers (18-43 years of age) were compared. $AUC_{0\text{-}inf}$ increased by 6.8% and C_{max} decreased by 2.1% in the elderly group, compared to the younger group.

Renal impairment

In subjects with mild (creatinine clearance ≥ 50 - < 80 mL/min) - CKD stage 2 and moderate (creatinine clearance ≥ 30 - < 50 mL/min) - CKD stage 3 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 (see PRECAUTIONS).

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 (see PRECAUTIONS). In patients with moderate hepatic impairment (Child Pugh Class B, avanafil C_{max} was approximately 51% lower and AUC was 11% higher compared to subjects with normal hepatic function. 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.

CLINICAL TRIALS

SPEDRA when taken on demand up to once daily is effective in improving erectile function in men with erectile dysfunction (ED). In clinical studies assessing patients' ability to engage in successful and satisfying sexual activity, SPEDRA demonstrated highly statistically significant improvement compared to placebo.

SPEDRA was evaluated in 4 randomised, double-blind, placebo-controlled, parallel group trials of up to 3 months in duration in patients with erectile dysfunction in the general population, as well as with the following aetiologies; patients with Type 1 or Type 2 diabetes, and in patients following bilateral nerve-sparing radical prostatectomy. The 4th study, a phase 4 trial, evaluated the onset of action of SPEDRA 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 SPEDRA, which was taken as needed at doses of 50 mg (one study only), 100 mg, and 200 mg (all four studies). Patients were instructed to take one dose of study medication approximately 30 minutes prior to initiation of sexual activity. In addition, a subset of patients from 2 of these trials were enrolled into an open-label extension trial with 493 patients receiving SPEDRA for at least 6 months and 153 patients for at least 12 months. Patients were initially assigned to SPEDRA 100 mg and at any point during the trial, they could request to have their dose of SPEDRA increased to 200 mg or decreased to 50 mg based on their individual response to treatment. In total, 536 (approximately 75%) patients increased their dose to 200 mg and 5 (less than 1%) patients reduced their dose to 50 mg.

In the phase 4 study (time to onset study), patients were encouraged to attempt sexual intercourse approximately 15 minutes after dosing, to assess the onset of the erectile effect of SPEDRA, taken on an as needed basis, at a 100 and 200 mg dose.

Food and alcohol were not restricted in all trials.

Several assessment questionnaires were used to measure the primary effect of SPEDRA in patients with erectile dysfunction. The 3 primary outcome measures were the erectile function domain of the International Index of Erectile Function (IIEF) and Questions 2 and 3 from Sexual Encounter Profile (SEP). The IIEF is a 4-week recall questionnaire that was administered at baseline and at 4-week intervals during treatment. The IIEF erectile function domain has a 30-point total score, where the higher scores reflect better erectile function. The SEP included diary-based measures of erectile function. SEP Question 2 assessed the ability to penetrate the partner's vagina, and SEP Question 3 assessed the ability to maintain the erection. Patients recorded information regarding each sexual attempt made throughout the trial.

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

Individual study results are presented below.

<u>Efficacy in the General Erectile Dysfunction (ED) Population:</u>

SPEDRA was evaluated in 646 men with ED of various aetiologies (organic, psychogenic, mixed). The mean age was 55.7 years (range 23 to 88 years). The population was 85.6% White, 13.2% Black, 0.9% Asian, and 0.3% of other races. The mean duration of ED was approximately 6.5 years. SPEDRA at doses of 50 mg, 100 mg, and 200 mg demonstrated statistically significant improvements in all 3 primary efficacy variables relative to placebo (see Table 1).

Table 1: Mean Change from Baseline for Primary Efficacy Variables in General ED Population (Study 1)

	Placebo (N=155)	SPEDRA 50 mg (N=154)	SPEDRA 100 mg (N=157)	SPEDRA 200 mg (N=156)
IIEF EF Domain Score				
Endpoint	15.3	18.1	20.9	22.2
Change from baseline†	2.9	5.4	8.3	9.5
p-value*	-	0.0014	<0.0001	<0.0001
Vaginal Penetration (SEP2)				
Endpoint	53.8%	64.3%	73.9%	77.3%
Change from baseline†	7.1%	18.2%	27.2%	29.8%
p-value*	-	0.0009	<0.0001	<0.0001
Successful Intercourse (SEP3)				
Endpoint	27.0%	41.3%	57.1%	57.0%
Change from baseline†	14.1%	27.8%	43.4%	44.2%
p-value*	-	0.0002	<0.0001	<0.0001

† Least-square estimate from ANCOVA model

* comparison to placebo for change from baseline

Efficacy in ED patients with Diabetes Mellitus

SPEDRA was evaluated in ED patients (n=390) with type 1 or type 2 diabetes mellitus. The mean age was 58 years (range 30 to 78 years). The population was 80.5% White, 17.2% Black, 1.5% Asian, and 0.8% of other races. The mean duration of ED was approximately 6 years. In this trial, SPEDRA at doses of 100 mg and 200 mg demonstrated statistically significant improvements in all 3 primary efficacy variables as measured by the erectile function domain of the IIEF questionnaire; SEP2 and SEP3 (see Table 2).

Table 2: Mean Change From Baseline for Primary Efficacy Variables in ED Population with Diabetes Mellitus (Study 2)

	Placebo (N=127)	SPEDRA 100 mg (N=126)	SPEDRA 200 mg (N=126)
IIEF EF Domain Score			
Endpoint	13.2	15.8	17.3
Change from baseline†	1.8	4.5	5.4
p-value*	-	0.0017	<0.0001
Vaginal Penetration (SEP2)			
Endpoint	42.0%	54.0%	63.5%
Change from baseline†	7.5%	21.5%	25.9%
p-value*	-	0.0004	<0.0001
Successful Intercourse (SEP3)			
Endpoint	20.5%	34.4%	40.0%
Change from baseline†	13.6%	28.7%	34.0%
p-value*	-	<0.0001	<0.0001

† least-square estimate from ANCOVA model

* comparison to placebo for change from baseline

Efficacy in ED Patients following bilateral nerve-sparing radical prostatectomy

SPEDRA was evaluated in ED patients (n=298) following bilateral nerve-sparing radical prostatectomy. The mean age was 58 years (range 30 to 78 years). Across all treatment groups,

the erectile dysfunction severity at baseline was mild for 9.1% of subjects, moderate for 19.5% of subjects, and severe for 71.5% of subjects. The majority of the subjects were White (81.5%). The mean duration of post-surgery erectile dysfunction was 18.7 months.

In adult male subjects with erectile dysfunction following bilateral nerve-sparing radical prostatectomy, SPEDRA treatment at both doses tested (100 mg and 200 mg) was associated with statistically significant improvements in all three co-primary endpoints of erectile function relative to placebo.

Table 3: Mean Change From Baseline for Primary Efficacy Variables in ED Population following bilateral nerve-sparring radical prostatectomy

Study TA 303	Placebo (n= 96)	SPEDRA 100 mg (n=94)	SPEDRA 200 mg (n=96)
IIEF EF Domain Score			
Endpoint	9.3 (5.51)	12.6 (8.08)	14.7 (8.65)
Change from baseline†	1.2 (1.16)	4.7 (1.18)	6.2 (1.11)
p-value*	0.2964	<0.0001	<0.0001
Vaginal Penetration (SEP2)			
Endpoint	19.7 (32.58)	32.5 (38.74)	40.8 (40.79)
Change from baseline†	7.5 (3.68)	22.3 (3.66)	27.7 (3.48)
p-value*	0.0417	<0.0001	<0.0001
Successful Intercourse (SEP3)			
Endpoint	8.9 (20.54)	23.4 (35.03)	26.4 (35.03)
Change from baseline†	13.9 (3.42)	28.0 (3.54)	29.4 (3.33)
p-value*	<0.0001	<0.0001	<0.0001

† least-square estimate from ANCOVA model
* comparison to placebo for change from baseline

Phase 4 study - Time to Onset Study in the ED Population

SPEDRA was evaluated in 440 subjects with ED including diabetics (16.4%) and subjects with severe ED (41.4%) in a randomised, double-blind, parallel, placebo-controlled study of 2 months' duration. The mean age was 58.2 years (range 24 to 86 years). The population was 75.7% White, 21.4% Black, 1.6% Asian, and 1.4% of other races. Subjects were encouraged to attempt intercourse approximately 15 minutes after dosing and used a stopwatch for measurement of time to onset of erection, defined as the time to the first occurrence of an erection sufficient for vaginal penetration.

SPEDRA 100 mg and 200 mg demonstrated statistically significant improvements relative to placebo in the primary efficacy variable, percentage of all attempts resulting in an erection sufficient for penetration at approximately 15 minutes after dosing followed by successful intercourse (SEP3). Refer to Table 4 below.

Table 4: Percentage of All Attempts Resulting in an Erection Sufficient for Penetration at Approximately 15 Minutes After Dosing Followed by Successful Intercourse (SEP3) During the 8-Week Treatment Period in the Time to Onset of Effect

	Placebo (N=136)	SPEDRA 100mg (N=139)	SPEDRA 200mg (N=139)
Percentage of Successful Intercourse (SEP3)			
Mean	14.9	25.9	29.1
Median	0.0	11.1	13.3
p-value*	-	0.001	< 0.001

* comparison to placebo using rank-ANCOVA model

INDICATIONS

Treatment of erectile dysfunction in adult males.

CONTRAINDICATIONS

- Co-administration with nitrates, nitric oxide donors, or organic nitrites in any form either regularly or intermittently. Drugs which must not be used concomitantly include, but are not limited to, glyceryl trinitrate (injection, tablets, sprays or patches), isosorbide salts, sodium nitroprusside, amyl nitrite, nicorandil or organic nitrates in any form. Consistent with the effects of PDE inhibition on the nitric oxide / cGMP–pathway, PDE5 inhibitors may potentiate the hypotensive effects of nitrates.
- Patients in whom sexual intercourse is inadvisable due to cardiovascular risk factors (see PRECAUTIONS). The possibility of undiagnosed cardiovascular disorders in men with erectile dysfunction should be considered before prescribing this medicine.
- Co-administration with guanylate cyclase stimulators such as riociguat as it may lead to potentially life-threatening symptomatic hypotension.
- Patients with the following cardiac conditions:
    - unstable angina, angina with sexual intercourse, or congestive heart failure categorised as New York Heart Association Class 2 or greater
    - in the last 6 months have suffered from a myocardial infarction, stroke, or life-threatening arrhythmia or coronary revascularisation
    - have resting hypotension (blood pressure < 90/50 mmHg) or hypertension (blood pressure > 170/100 mmHg).
- Patients with severe hepatic impairment (Child-Pugh C).
- Patients with severe renal impairment (creatinine clearance < 30 mL/min) - CKD stage 4 or end stage renal failure (CKD Stage 5).
- Patients who have loss of vision in one eye because of non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this episode was in connection with previous exposure to a PDE5 inhibitor (see PRECAUTIONS).
- 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 INTERACTIONS).
- Patients with a known hypersensitivity to avanafil or to any ingredient of the tablet.

PRECAUTIONS

Before treatment with SPEDRA

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: there is a potential for cardiac risk during sexual activity in patients with pre-existing cardiovascular disease. Therefore treatments for ED, including SPEDRA, should not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status (see CONTRAINDICATIONS).

Patients with left ventricular outflow obstruction, e.g. aortic stenosis and idiopathic hypertrophic subaortic stenosis, and those with severely impaired autonomic control of blood pressure can be particularly sensitive to the action of vasodilators, including SPEDRA.

As with other PDE5 inhibitors, SPEDRA has vasodilator properties, resulting in mild and transient decreases in blood pressure and may augment the blood pressure-lowering effect of other anti-hypertensive medications. SPEDRA 200 mg resulted in transient decreases in sitting blood pressure in healthy volunteers of 8.0 mmHg systolic and 3.3 mmHg diastolic, with the maximum decrease observed at 1 hour after dosing. While this normally would be expected to be of little consequence in most patients, prior to prescribing SPEDRA, physicians should carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

SPEDRA potentiates the hypotensive effect of nitrates. Therefore co-administration of SPEDRA and nitrates, nitric oxide donors, or organic nitrites is contraindicated (see CONTRAINDICATIONS).

Concomitant use of alpha-blockers

Physicians should discuss with patients the potential for SPEDRA to augment the blood–pressure lowering effect of alpha blockers (e.g. prazosin, tamsulosin, terazosin) and other antihypertensive medications (see PRECAUTIONS and PHARMACOLOGY). Caution is advised when PDE5 inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including SPEDRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients concomitant use of these two classes can lower blood pressure significantly leading to symptomatic hypotension (e.g. dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating treatment with SPEDRA. Patients who demonstrate haemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of SPEDRA.
- In those patients who are stable on alpha-blocker therapy, SPEDRA 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 SPEDRA.

The safety of combined use of SPEDRA and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive medicinal products (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Decreased or Sudden Hearing Loss

Patients should be advised to stop taking PDE5 inhibitors, including SPEDRA, 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 association with 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 (see ADVERSE EFFECTS).

Visual problems

Visual defects and cases of non-arteritic anterior ischaemic optic neuropathy (NAION) have been reported in connection with the intake of PDE5 inhibitors. Physicians should advise patients to stop use of all PDE5 inhibitors, including SPEDRA, and seek medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision including permanent loss of vision that has been reported rarely post-marketing in association with the use of all PDE5 inhibitors. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Use of SPEDRA is contraindicated in patients who have loss of vision in one eye

because of NAION, regardless of whether this episode was in connection with previous exposure to a PDE5 inhibitor (see CONTRAINDICATIONS).

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.

Priapism

Prolonged erection lasting 4 hours or more (priapism) has been reported with other PDE5 inhibitors. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

SPEDRA 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).

Effect on bleeding

In vitro studies with human platelets indicate that PDE5 inhibitors including avanafil 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 SPEDRA to patients with bleeding disorders or active peptic ulceration. Therefore, SPEDRA should be administered to such patients only after careful benefit-risk assessment.

Concomitant use of CYP3A4 inhibitors

SPEDRA metabolism is principally mediated by the CYP450 isoform 3A4 (CYP3A4). Inhibitors of CYP3A4 may reduce SPEDRA clearance and increase plasma concentrations of SPEDRA. For patients taking concomitant strong CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, voriconazole, nefazodone, nelfinavir, saquinavir and telithromycin), SPEDRA is contraindicated (see CONTRAINDICATIONS).

For patients taking concomitant moderate CYP3A4 inhibitors (including erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil), the maximum recommended dose of SPEDRA is 100 mg, and not to exceed once every 48 hours (see INTERACTIONS WITH OTHER MEDICINES).

Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice are likely to increase SPEDRA exposure.

Illicit drugs

The use of avanafil with illicit drugs has not been studied.

Renal Impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance ≥ 30 to < 80 mL/min) - CKD stage 2-3. However patients in this group enrolled in phase 3 studies showed decreased efficacy compared to those with normal renal function. The pharmacokinetics of SPEDRA in patients with severe renal disease or end stage renal failure (CKD stage 5) has not been studied.Hence, SPEDRA is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min, CKD stage 4) and end stage renal failure (CKD Stage 5) (See CONTRAINDICATIONS and PHARMACOKINETICS).

Hepatic Impairment

Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum efficacious dose and adjust dosage based on tolerance.

The pharmacokinetics of SPEDRA in patients with severe hepatic disease (Child Pugh class C) has not been studied; do not use SPEDRA in such patients (see CONTRAINDICATIONS and PHARMACOKINETICS).

Concomitant use of alcohol

Consumption of alcohol in combination with SPEDRA can increase the potential for symptomatic hypotension (see PHARMACODYNAMICS and INTERACTIONS WITH OTHER MEDICINES).

Patients should be advised that substantial consumption of alcohol in combination with SPEDRA 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.

Neurological disorders

SPEDRA has not been evaluated in patients with erectile dysfunction due to spinal cord injury or other neurological disorders.

Effects on Fertility

There was no effect on sperm motility or morphology after single 200 mg oral doses of SPEDRA in healthy volunteers. Currently, no data on spermatogenesis on healthy adult males or adult males with mild ED are available.

There were no effects on fertility or sperm parameters in male rats at doses of SPEDRA up to 300 mg/kg/day (in male rats 17 times human exposure based on unbound AUC at a dose of 200 mg). There was a decrease in fertility and sperm motility, altered estrous cycles, and an increased percentage of abnormal sperm at doses of 1000 mg/kg/day, a dose which also caused parental toxicity in the treated males and females. There were no clinically relevant 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 SPEDRA for 9 months at exposures 127 times human exposure at the Maximum Recommended Human Dose (MRHD).

Use in Pregnancy

Pregnancy Category B3

SPEDRA is not indicated for use by women. There are no data from the use of SPEDRA in pregnant women. Rat studies do not indicate direct harmful effects with respect to pregnancy, embryo/foetal development, parturition, or postnatal development at doses up to 300 mg/kg/day in rats (relative exposure at least 138 times based on unbound AUC). Foetal and pup weight was reduced in rats that received at least 600 mg/kg/day during organogenesis, and remained decreased after weaning (relative exposure at least 435 times based on unbound AUC). Similarly, maternotoxic doses of avanafil in pregnant rabbits (240 mg/kg/day during organogenesis; relative exposure 44 times based on unbound AUC) elicited an increase in late resorptions. Furthermore, there was an increased incidence of visceral variations (extra subclavian artery) in the offspring of rabbits that received at least 60 mg/kg/day avanafil (relative exposure approximately 7 times based on mg/m^2).

Use in Lactation

SPEDRA is not indicated for use in women. There are no data on the use of SPEDRA during breastfeeding.

Paediatric Use

No data available.

Use in the Elderly

Of the total number of subjects in clinical studies of SPEDRA, approximately 23% were 65 and over. No overall differences in safety and efficacy were observed between subjects over 65 years of age compared to younger subjects. Data on patients older than 70 years is limited as there were few patients in this age group included in the trials. Dose adjustment is not warranted based on age alone, however a greater sensitivity to medication should be considered in some older individuals.

Genotoxicity

SPEDRA was not mutagenic in bacterial reverse mutagenesis assays and was not clastogenic in chromosome aberration assays using Chinese Hamster Ovary and lung cells, but was positive in the mouse lymphoma mutagenesis assay in the presence of metabolic activation. However avanafil was negative in the *in-vivo* mouse micronucleus assay and did not affect DNA repair when

tested in the rat unscheduled DNA synthesis assay. The weight of evidence indicates that avanafil is unlikely to be genotoxic.

Carcinogenicity

SPEDRA was not carcinogenic to CD-1 mice when administered daily at doses of 100, 200, or 600 mg/kg/day orally by gavage for up to 91 weeks (approximately 11 times the MRHD on an AUC basis) or to Sprague Dawley rats when administered daily at doses of 100, 300, or 1000 mg/kg/day orally by gavage for at least 100 weeks (approximately 142 times for males and 589 times for females above the MRHD for the high dose group on an unbound AUC basis).

Effects on ability to drive and operate machinery

As dizziness and visual disturbances were reported in clinical trials with SPEDRA, patients should be aware of how they react to SPEDRA before driving or operating machinery.

INTERACTIONS WITH OTHER MEDICINES

Potential for Pharmacodynamic Interactions with SPEDRA

Nitrates

Administration of SPEDRA to patients who are using any form of organic nitrate or nitric oxide donor (such as amyl nitrite), is contraindicated. In a clinical pharmacology trial, SPEDRA was shown to potentiate the hypotensive effect of nitrates. This is thought to result from the combined effects of nitrates and SPEDRA on the nitric oxide/cGMP pathway.

In a patient who has taken SPEDRA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of SPEDRA before nitrate administration is considered. The likelihood of a significant and potentially dangerous drop in blood pressure is increased. In such circumstances, nitrates should only be administered under close medical supervision with appropriate haemodynamic monitoring (see CONTRAINDICATIONS).

Medicinal products reducing systemic blood pressure

As a vasodilator, SPEDRA may reduce systemic blood pressure. If SPEDRA is used in combination with another medicine which reduces systemic blood pressure, the additive effects may result in symptomatic hypotension (e.g. dizziness, light-headedness, syncope or near-syncope). In phase 3 clinical trialsno events of “hypotension” but occasional episodes of “dizziness” were observed (see ADVERSE EFFECTS). One episode of “syncope” was observed on placebo and one episode on 100 mg of SPEDRA in phase 3 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 SPEDRA.

Alpha-blockers

Caution is advised when PDE5 inhibitors are co-administered with 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 SPEDRA 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 SPEDRA dosing (see PRECAUTIONS).

In patients receiving stable tamsulosin treatment, the placebo-subtracted mean maximum decreases in standing and supine systolic blood pressure following SPEDRA 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 SPEDRA dosing (see

PRECAUTIONS). There were no reports of syncope or other severe adverse events associated with lowering of blood pressure on either cohort of subjects.

Antihypertensives other than alpha-blockers

PDE5 inhibitors are mild systemic vasodilators, hence SPEDRA may augment the blood pressure lowering effects of antihypertensive agents. A clinical study was conducted to assess the effect of SPEDRA on the potentiation of the blood pressure-lowering effects of selected antihypertensive medications (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 SPEDRA was co-administered. There was a statistically significant difference in maximum decrease from baseline in supine diastolic blood pressure with enalapril and SPEDRA only, which returned to baseline 4 hours after the dose of SPEDRA. In both cohorts, one subject experienced a decrease in blood pressure without symptoms of hypotension, which resolved within 1 hour of onset. SPEDRA had no effect on the pharmacokinetics of amlodipine, but amlodipine increased the maximum and total exposure of SPEDRA by 28% and 60%, respectively.

Caution should be exercised when prescribing SPEDRA in combination with antihypertensive agents.

Riociguat

Preclinical studies showed additive systemic blood pressure lowering effects 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 avanafil is contraindicated (see CONTRAINDICATIONS).

Alcohol

Both alcohol and PDE5 inhibitors, including SPEDRA, act as vasodilators. When vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol in combination with SPEDRA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache.

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 (see PRECAUTIONS).

Potential for other Drugs to affect SPEDRA

SPEDRA is a substrate of, and predominantly metabolised by, CYP3A4. Studies have shown that medicines that inhibit CYP3A4 can increase SPEDRA exposure (see PRECAUTIONS).

Strong CYP3A4 Inhibitors

Ketoconazole (400 mg daily), a selective and highly potent inhibitor of CYP3A4, increased SPEDRA 50 mg single-dose C_{max} and exposure (AUC) equal to 3-fold and 14-fold respectively and prolonged the half-life of SPEDRA to approximately 9 hours.

Ritonavir (600 mg twice daily), a highly potent CYP3A4 inhibitor, which also inhibits CYP2C9, increased SPEDRA 50 mg single-dose C_{max} and AUC equal to approximately 2-fold and 13-fold, and prolonged the half-life of SPEDRA to approximately 9 hours.

Other strong inhibitors of CYP3A4 (e.g. itraconazole, voriconazole, clarithromycin, nefazodone, saquinavir, nelfinavir, indinavir, atazanavirr, and telithromycin) would be expected to have similar effects. Consequently, co-administration of SPEDRA with potent CYP3A4 inhibitors is contraindicated (see CONTRAINDICATIONS).

Moderate CYP3A4 Inhibitors

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, increased SPEDRA 200 mg single-dose C_{max} and AUC equal to approximately 2-fold and 3-fold, respectively, and prolonged the half-life of SPEDRA 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 SPEDRA is 100 mg, not to exceed once every 48 hours for patients taking concomitant moderate CYP3A4 inhibitors (see PRECAUTIONS).

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

CYP3A4 substrate

Amlodipine (5 mg daily) increased SPEDRA 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 SPEDRA on amlodipine plasma levels.

Although specific interactions of SPEDRA 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, phenobarbitone and rifampicin) on the pharmacokinetics and efficacy of SPEDRA has not been evaluated. The concomitant use of SPEDRA and a CYP inducer is not recommended as it may decrease the efficacy of SPEDRA.

Potential for SPEDRA to affect other drugs

Cytochrome P450 Inhibition

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

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

Warfarin

A single 200 mg dose of SPEDRA did not cause changes in PT or INR, and did not affect collagen-induced platelet aggregation or the AUC or C_{max} of R- or S-warfarin, a 2C9 substrate.

Cytochrome P450 Induction

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

Transporters

In-vitro results showed that SPEDRA is a weak P-gp substrate. Digoxin efflux was inhibited by SPEDRA in MDCK cells, but this inhibition did not appear to be due to inhibition of human P-glycoprotein. The potential of SPEDRA to interfere with the transport of other medicinal products mediated by P-gp, particularly in the intestinal tract, is not known.

In-vitro data indicate that at therapeutic doses, SPEDRA would not inhibit OCT1, OCT2, OATP1B1, OATP1B3, OAT3 or BSEP. SPEDRA inhibited BCRP with IC_{50} and K_i values of approximately 1 µM and would therefore likely inhibit BCRP in the intestinal tract, but this inhibition is unlikely to be clinically relevant. SPEDRA is unlikely to inhibit BCRP in other tissues.

ADVERSE EFFECTS

The safety profile of SPEDRA is based on 2436 subjects exposed to SPEDRA 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 SPEDRA-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.

In five randomised, double-blind, placebo-controlled trials involving 2,000 patients, the mean age of patients was 57.1 years (range from 23 to 88 years). 81.7 % of patients were White, 16.1% were Black, 1.1% Asian, and < 1% Hispanic or other races. 48.8% were current or previous smokers. 31.3% had diabetes mellitus. The discontinuation rate due to adverse events for patients treated with SPEDRA 50 mg, 100 mg, or 200 mg was 1.4%, 2.2%, and 2.2%, respectively, compared to 1.4% for placebo-treated patients.

Table 5 presents Treatment-Emergent Adverse Events (TEAEs) reported when SPEDRA was taken as recommended (on an as-needed basis) from these 5 clinical trials.

Table 5: Treatment-Emergent Adverse Events (TEAE) Reported by ≥ 1% of Patients Treated with SPEDRA From 5 Placebo-controlled Clinical Trials (TA-05, TA-301, TA-302, TA-303 and TA-501).

TEAE	Placebo (N = 592)	SPEDRA 50 mg (N = 217)	SPEDRA 100 mg (N = 594)	SPEDRA 200 mg (N = 597)
Headache	1.4%	5.1%	5.7%	10.4%
Flushing	0.0%	3.2%	3.5%	4.4%
Nasal congestion	0.8%	1.8%	2.4%	2.3%
Nasopharyngitis	2.2%	0.9%	2.2%	3.2%
Back pain	0.8%	3.2%	1.7%	1.2%
Constipation	0.2%	1.4%	0.0%	0.0%
Dyspepsia	0.2%	0.5%	0.5%	1.0%
Nausea	0.2%	0.0%	0.5%	1.0%
Bronchitis	0.8%	1.4%	0.2%	0.8%
Influenza	0.0%	0.5%	1.3%	0.5%
Sinusitis	0.7%	0.0%	1.0%	0.7%
Upper respiratory	1.7%	1.8%	1.5%	1.7%
Sinus congestion	0.3%	0.5%	0.5%	1.2%
Rash	0.2%	1.4%	0.0%	0.2%
Hypertension	0.5%	0.5%	1.2%	0.5%

In an open-label, long-term extension study of two of these randomised, double-blind, placebo-controlled trials, the total duration of treatment was up to 52 weeks. Among the 712 patients who participated in this open-label extension study, the mean age of the population was 56.4 years (range from 23 to 88 years). The discontinuation rate due to adverse reactions for patients treated with SPEDRA (50 mg, 100 mg, or 200 mg) was 2.8% (see CLINICAL TRIALS).

Table 6 presents TEAEs reported when SPEDRA was taken as recommended (on an as-needed basis) in this open-label extension trial.

Table 6: Treatment-Emergent Adverse Events (TEAE) Reported by ≥ 1% of Patients Treated With SPEDRA in an Open- Label Extension Trial

Treatment Emergent Adverse Event	SPEDRA (N= 711)
Headache	5.6%
Flushing	3.5%
Nasopharyngitis	3.4%
Nasal congestion	2.1%
Influenza	1.5%
Upper respiratory tract infection	1.5%

Back pain	1.5%
Sinusitis	1.4%
Dizziness	1.3%
Hypertension	1.3%
Diarrhoea	1.3%
Bronchitis	1.1%
Arthralgia	1%

Adverse reactions reported by < 2% of patients treated with SPEDRA in all phase 3 studies

Except for headache (6.9%) and flushing (5.7%) the incidence of all the other adverse reactions (refer to the Table 7 for a complete list) was <2%.

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 (≥ .1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7: Adverse Reactions Observed In Placebo-Controlled Clinical Trials According To The MedDRA Frequency Convention

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
Gastrointestinal disorders		Dyspepsia Nausea Vomiting Stomach discomfort	Dry mouth Gastritis Abdominal pain lower Diarrhoea
Skin and subcutaneous tissue disorders			Rash

Adverse reaction (MedDRA Preferred Term)			
System Organ Class	**Common**	**Uncommon**	**Rare**
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

Post-marketing experience

In coherence with the safety profile that emerged from the clinical trials, headache and flushing/hot flush are the most reported adverse reactions in the post-marketing experience (both frequency not known).

DOSAGE AND ADMINISTRATION

Use in adult men

The recommended dose is 100 mg taken as needed approximately 15-30 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The lowest dose that provides benefit should be used and the additional efficacy of the 200 mg dose could be limited. The maximum recommended dosing frequency is once per day. SPEDRA is intended for use prior to anticipated sexual activity. In order for SPEDRA to be effective, sexual stimulation is required.

SPEDRA may be taken with or without food. If SPEDRA is taken with food, the onset of activity may be delayed compared to the fasted state.

In those patients who are stable on alpha-blocker therapy, SPEDRA should be initiated at the lowest dose of 50 mg (see PRECAUTIONS, Concomitant use with alpha blockers).

Use in Older men (≥ 65 years old)

Dose adjustments are not required in older patients. However, it should be considered that co-morbidities increase with age.

Patients with Renal impairment

Dose adjustments are not required in patients with mild to moderate renal impairment (creatinine clearance ≥ 30 mL/min) - CKD Stage 2-3. The pharmacokinetics of SPEDRA in patients with severe renal disease or on renal dialysis (CKD stage 4-5) has not been studied; SPEDRA is contraindicated in these patients (see CONTRAINDICATIONS).

Patients with Hepatic impairment

Patients with mild to moderate hepatic impairment (Child-Pugh class A or B) should initiate treatment with the minimum effective dose and adjust dosage based on tolerance.
The pharmacokinetics of SPEDRA in patients with severe hepatic disease (Child-Pugh class C) has not been studied; SPEDRA is contraindicated in these patients (see PHARMACOKINETICS and CONTRAINDICATIONS).

Use in men with diabetes

Dose adjustments are not required in diabetic patients.

Concomitant use of CYP3A4 inhibitors

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

Co-administration of SPEDRA with potent CYP3A4 inhibitors (including ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin) is contraindicated (see CONTRAINDICATIONS).

OVERDOSAGE

A single dose of up to 800 mg of SPEDRA has 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. The risk of QT prolongation increases with higher doses of avanafil (see Pharmacodynamics, Effects on Cardiac Electrophysiology) and there is no data on the effect of SPEDRA 200 mg on QT prolongation. Cardiac risk factors or concomitant medications that prolong QT interval or increase avanafil exposure may increase the risk of QT prolongation.

In case of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as SPEDRA is highly bound to plasma proteins and it is not eliminated in the urine. In the case of overdose, immediately contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

The 50 mg tablets are pale yellow, oval tablets debossed with ‘50’ on one side. They are presented in blister packs of 1, 2, 4, 8 and 12 tablets per carton.

The 100 mg tablets are pale yellow, oval tablets debossed with ‘100’ on one side. They are presented in blister packs of 1, 2, 4, 8 and 12 tablets per carton.

The 200 mg tablets are pale yellow, oval tablets debossed ‘200’ on one side. They are presented in blister packs of 1, 2, 4, 8 and 12 tablets per carton.

All blisters are composed of transparent PVC/PCTFE film and aluminium foil.

Not all pack sizes may be marketed.

Store below 25ºC.

NAME AND ADDRESS OF THE SPONSOR

A. Menarini Australia Pty Ltd

Level 8, 67 Albert Ave
Chatswood NSW 2067 Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

5 April 2016