EU RISK MANAGEMENT PLAN FOR SPEDRA (AVANAFIL)

RMP version to be assessed as part of this application:

RMP Version number: 6.0

Data lock point for this RMP: 21-Jun-2024

Date of final sign off: 05-Sep-2024

Rationale for submitting an updated RMP:
The RMP has been updated according the the PRAC recommendation received in the context of the latest two PSUSA procedures (EMEA/H/C/PSUSA/00010066/202006 and EMEA/H/C/PSUSA/00010066/202306) in which the MAH was requested to update the RMP according to the GVP Module V on Risk Management Systems rev 2. Since neither additional pharmacovigilance activities nor additional risk minimisation measures are in place, the list of safety concerns in the RMP has been updated and the proposed list is currently empty.

Summary of significant changes in this RMP:

The list of safety concerns has been updated as follows:
- “Cardiovascular risk in patients with pre-existing overt and covert cardiovascular disease” and “Prolonged erection (priapism)” previously classified as important identified risks have been removed from the safety concerns list;
- “Hypotension/increased hypotensive effect”, “Non-arteritic anterior ischaemic optic neuropathy” and “Sudden hearing loss” previously classified as important potential risks have been removed from the safety concerns list;
- “Very elderly males > 70 years of age”, “Use in subject with severe renal or hepatic failure”, “Adults males with ED due to spinal cord injury”, “Patients with retinitis pigmentosa” and “Patients with bleeding disorders or active peptic ulceration” previously classified as missing information have been removed from the safety concerns list.

Therefore, Part II Module SVII and Module SVIII, Part V and Part VI have been updated accordingly.

The new RMP template (EMA/PRAC/613102/2015 rev 2), according with the revised GVP Module V (rev 2) has been adopted.

The content of the latest RMP version (v 5.1), elaborated according to the old GVP Module V format, has been considered and updated.

The other changes are of minor nature.

Other RMP versions under evaluation:

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 5.1

Approved with procedure: EMEA/H/C/002581/II/0027
Date of approval (opinion date): 09/11/2017

QPPV name: Dr. Francesco Sarlo, MD

[redacted]

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

Not available.

LIST OF ABBREVIATIONS

ABBREVIATION	WORDING DEFINITION
5-ARIs	5-a Reductase Inhibitors
ADR	Adverse drug reaction
AUC	Area under (the plasma concentration) curve
BCRP	Breast Cancer Resistance Protein
b.i.d	Twice daily (bis in die)
BSEP	Bile Salt Export Pump
Cmax	Maximum plasma concentration
CI	Confidence interval
CYP3A4	Cytochrome P3A4
CYP450	Cytochrome P450 group of liver metabolising enzymes
cGMP	Cyclic guanosine monophosphate
DILI	Drug induced liver injury
ED	Erectile dysfunction
EPAR	European Public Assessment Report
ERG	Electroretinogram
EU	European Union
EV	Eudravigilance
GD	Gestational Day
HIV	Human immunodeficiency virus
LD_{50}	Lethal Dose
LUTS	Lower urinary tract symptoms
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligram
MPOA	Medial Preoptic Area
MRHD	Maximum Recommended Human Dose
NAION	Non-arteritic anterior ischaemic optic neuropathy
NOAL	No observed adverse effect level
NOEL	No observed effect level
OAT	Organic Anion Transporter
OCT	Organic Cation Transporter
PDE5	Phosphodiesterase Type 5
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PSUSA	Periodic safety update single assessment
PT	(MedDRA) Preferred Term
PV	Pharmacovigilance
RMP	Risk Management Plan
SOC	(MedDRA) System Organ Class
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event

PART I. PRODUCT(S) OVERVIEW

Table Part I–1 – Product Overview

Active substance(s) (INN or common name)	Avanafil
Pharmacotherapeutic group(s) (ATC Code)	Urologicals, drugs used in erectile dysfunction (ATC code: G04BE10)
Marketing Authorisation Applicant	Menarini International Operations Luxembourg S.A.
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Spedra
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Avanafil is a highly selective and potent, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5.
	Summary of mode of action: 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.
	Important information about its composition: The active ingredient is obtained by chemical synthesis. Avanafil do not contain excipients of human or animal origin, or any “novel” excipients.
Hyperlink to the Product Information	- Product Information Spedra 50 mg tablets - Product Information Spedra 100 mg tablets - Product Information Spedra 200 mg tablets
Indication(s) in the EEA	Current: Treatment of erectile dysfunction in adult men. In order for avanafil to be effective, sexual stimulation is required.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 100 mg taken as needed approximately 15 to 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 maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 50 mg, 100 mg and 200 mg tablet
	Proposed: Not applicable
Is / will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

PART II: MODULE SI. - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Treatment of erectile dysfunction (ED) in adult men

Incidence

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual performance. ED has a significant medical and social impact due to its high prevalence, costs, and implications for the quality of life for many men (and their partners). Cross-sectional epidemiological studies from around the world reveal that 30% to 50% of men aged 40 to 70 years report some degree of ED. About 150 million men worldwide meet the definition for ED. Age is the variable most associated with ED – between 40 and 70 years of age the incidence of moderate ED doubles from 17% to 34% and the incidence of severe ED triples from 5% to 15%. It is estimated that the prevalence of ED will continue to increase in line with increasing life expectancy with an estimated 328 million men worldwide affected by ED by 2025.

Prevalence

Normal human penile erectile function involves the coordination of psychological, hormonal, neurological, vascular, and anatomic factors; the disturbance of one or more being sufficient to cause ED. Around 80% of cases are believed to have an organic cause, the rest being psychogenic in origin. Most cases are believed to be multifactorial and secondary to disease, stress, trauma (such as spinal cord injury, pelvic and prostate surgery), or drug adverse effects that interfere with the coordinated psychological, neurological, endocrine, vascular, and muscular factors necessary for normal erections. Risk factors include increasing age, smoking, obesity, and sedentary lifestyle. The prevalence of ED also increases in people with diabetes mellitus, hypertension, heart disease, anxiety, and depression.

Demographics of the population in the proposed indication – age, gender, racial and / or ethnic origin and risk factors for the disease

Age
Erectile dysfunction is a significant and common medical problem. Recent epidemiologic studies suggest that approximately 10% of men aged 40-70 have severe or complete erectile dysfunction, defined as the total inability to achieve or maintain erections sufficient for sexual performance. An additional 25% of men in this age category have moderate or intermittent erectile difficulties. The disorder is highly age-dependent, as the combined prevalence of moderate to complete erectile dysfunction rises from approximately 22% at age 40 to 49% by age 70. Although less common in younger men, erectile dysfunction still affects 5%-10% of men below the age of 40. Findings from these studies show that erectile dysfunction impacts significantly on mood state, interpersonal functioning, and overall quality of life.

Gender
Erectile dysfunction is a dysfunction of the genital male organ.

Racial and / or ethnic origin

Data available in literature (Smith JF, et al., 2009) allow to understand that the rates of severe ED were lowest among asian and black men and highest among white, hispanic, and other thnic groups. The increased prevalence of moderate to severe ED among hispanic men was primarily explained by their higher prevalence of medical co-morbidities. Socioeconomic status played a lesser role.

For asian men, adjustment for lifestyle characteristics resulted in an increase in the odds of moderate-to-severe ED, due to the relatively low BMI and prevalence of tobacco use in this group.

Among black men, their lower odds of severe ED were mediated by self-reported health status and medical comorbidities. Even after adjustment for all of these factors, their odds for severe ED was significantly lower. The reasons or mechanisms that might account for this observation in black men remain unknown. While significant racial and ethnic differences in the odds of ED were observed, even after extensive adjustment for known or suspected risk factors residual confounding by unmeasured factors might yet explain these differences. Factors such as cultural perceptions of ED, quality and type of relationships, and construct of masculinity may all influence a self-reported history of erectile function (or dysfunction). Future studies can target these factors explicitly.

Risk factors for the disease

Erectile dysfunction primarily affects adult men, typically those aged 40 years and older. The prevalence of ED increases with age, with a significant proportion of men experiencing symptoms by their late 50s and 60s. While ED can affect men of all racial and ethnic backgrounds, certain populations may exhibit specific prevalence patterns or risk factors.

It is important to note that ED is often associated with underlying health conditions, such as diabetes, hypertension, heart disease, obesity, and metabolic syndrome. These conditions can increase the risk of developing ED and may influence treatment decisions. Additionally, lifestyle factors including smoking, excessive alcohol consumption, and physical inactivity can contribute to the development and progression of ED.

Lower urinary tract symptoms (LUTS) is another condition that seems associated with ED. This suggest early preventive assessment and follow-up of ED, because LUTS can lead to negative sexual symptoms. Also, emotional problems can influence erectile dysfunction problems. Depressive symptoms can be associated with ED. Additionally, many anti-depressive drugs increase risk of ED (e.g. some SSRIs like citalopram and sertraline), and patients with ED and depressive symptoms have less adherence to treatment for ED. Therefore, special attention should be given to this association when planning and assessing its treatments and also in the association that this variable has with other behavioural and clinical factors. It is important to consider that other drugs can have effect on erection: neuropsychiatric medications with high frequencies of ED include escitalopram, quetiapine, olanzapine, fluoxetine, venlafaxine, risperidone, aripiprazole, gabapentin, pregabalin, and oxycodone and 5-a Reductase Inhibitors (5-ARIs) as Finasteride and dutasteride drugs used against prostatic hypertrophy.

Other risk factor refers to neurogenic alteration. The MPOA (medial preoptic area), the paraventricular nucleus, and the hippocampus have been regarded as important integration centers for sexual drive and penile erection. Pathological processes in these regions, such as Parkinson’s disease, stroke, encephalitis, or temporal lobe epilepsy, are often associated with ED. Parkinsonism’s effect may be caused by the imbalance of the dopaminergic pathways.

Other lesions in the brain noted to be associated with ED are tumors, dementias, Alzheimer's disease, Shy-Drager syndrome, and trauma.
In men with a spinal cord injury, their erectile function depends largely on the nature, location, and extent of the spinal lesion. In addition to ED they may also have impaired ejaculation and orgasm.
It shall be also underlined that some pelvic surgeries (e.g. on prostate) can lead to lesions of the pudendal nerve that result in partial or total ED.

The main existing treatment options

The main existing treatment options for erectile dysfunction (ED) encompass a range of approaches tailored to the individual patient's needs and underlying causes. These include:

- **Lifestyle modifications:** Weight management, regular physical activity, smoking cessation, and limited alcohol consumption can improve overall health and potentially erectile function.
- **Psychological therapies:** Cognitive-behavioural therapy and sex therapy can address psychological factors contributing to ED.
- **Pharmacological treatments:**
    - Phosphodiesterase type 5 (PDE5) inhibitors, such as avanafil, are the first-line treatment for most men with ED. These medications enhance erectile function by increasing blood flow to the penis.
    - Other pharmacological options may include vasoactive drugs (intra-cavernous, transurethral or topical administration) and alpha-adrenergic blockers.
- **Hormonal treatments:** Testosterone replacement therapy is considered in cases of confirmed hypogonadism.
- **Vacuum erection devices:** These mechanical devices can induce erections but are generally considered second-line options.
- **Invasive treatments:** Surgical implants or vascular surgery may be considered in severe, refractory cases.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Erectile dysfunction (ED) is generally not a life-threatening condition, and its direct impact on mortality is limited. However, it can significantly impact a patient's quality of life, leading to psychological distress, relationship difficulties, and decreased self-esteem. The long-term consequences of untreated ED can include social isolation, depression, and anxiety. While ED itself does not directly increase the risk of mortality, it is often associated with underlying health conditions such as cardiovascular disease, diabetes, and metabolic syndrome, which can increase the risk of mortality.

Important co-morbidities

ED is primarily a disease of advancing age. The most important co-morbidity from a safety perspective when prescribing a PDE5 inhibitor is significant small vessel disease due to arteriosclerosis as a consequence of Type 1 or 2 diabetes mellitus, hypertension or dyslipidaemia. Men with arteriosclerosis also have an increased incidence of ED.
ED is additionally a known potential side effect of radical prostatectomy.

In double-blind clinical studies with avanafil, 668 (42.5%) patients had a co-morbidity of hypertension, 630 (40.1%) dyslipidaemia, 152 (9.7%) coronary artery disease, 195 (12.4%) other cardiovascular disease and 165 (10.5%) depression.

PART II: MODULE SII. - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

Toxicity

- Key issues identified from acute and repeat-dose toxicity studies

The single-dose toxicity of avanafil has been investigated in the mouse and rat by oral and intravenous administration and in the dog after oral administration.
Single oral administration of avanafil was well tolerated in mice and rats with the acute oral LD_{50} being greater than 2000 mg/kg in both species. The acute intravenous LD_{50} was greater than 40 mg/kg in the respective species. In Beagle dogs, escalating single oral doses of avanafil were also shown to be well tolerated at doses up to and including 2000 mg/kg. The effect of feeding or fasting on the toxicity of single oral doses of avanafil was examined in Beagle dogs. Fewer clinical signs were noted in the fasted animals than in the fed animals, but tachycardia occurred in both (fasted at 300 mg/kg and fed at 30, 100 and 300 mg/kg). The more pronounced effects in the fed animals were likely associated with the noticeably higher C_{max} and AUC values observed in these animals as compared to the fasted animals.

Repeat-dose toxicity studies have been performed on mice, rats and dogs.
Across the three species treated repeatedly with avanafil, the primary effects included decreases in body weight, increases in liver weight, and hepatocellular hypertrophy; the latter two findings being indicative of an adaptive response to extensive hepatic metabolism due to the administration of very high doses.

In mice, the primary findings following repeated oral administration avanafil for 13 weeks included: toxicity (pronounced adverse clinical signs and mortality) with decreased body weight and/or weight loss at the high dose, 2000 mg/kg/day, which required a drug holiday and a lowering of the dose to 1000 mg/kg/day; increased liver weight at 2000/1000 mg/kg/day; hepatocellular hypertrophy at 600 and/or 2000/1000 mg/kg/day) and minimal interstitial fibrosis, mineralization, lymphohistiocytic infiltration, and pigment in the heart at 600 and/or 2000/1000 mg/kg/day). The no-observed-effect-level (NOEL) was 200 mg/kg/day (corresponding to AUC values for avanafil of 5.51 and 14.6 μg·h/mL in males and females, respectively).
The findings in the heart are unique to mice, but the other changes are consistent with the toxicity profile in the other nonclinical species following repeated dosing.

A series of repeat-dose studies were conducted in rats. Following one-week of dosing, avanafil produced decreased body weight and weight gain (males at 300 mg/kg/day), significant increases in a-and b-wave amplitudes in electroretinograms (ERG) (females at 300 mg/kg/day), and increased liver weight (no microscopic correlate) and drug metabolizing enzymes (100 and/or 300 mg/kg/day). The no-observed-adverse-effect-level (NOAEL) was determined to be 100 mg/kg/day (corresponding to AUC values for avanafil of 0.896 and 10.3 μg·h/mL in males and females, respectively).
Two-weeks of dosing in rats produced only increased liver weight with no corresponding histopathologic changes (100 mg/kg/day and above) and increased drug metabolizing enzyme activities (300 and 1000 mg/kg/day). The NOAEL was considered

to be 1000 mg/kg/day (corresponding to AUC values for avanafil of 64.8 and 269 μg·h/mL in males and females, respectively).
Similarly, for male rats dosed for 28 days. the main effect was a significant increase in liver weight (1000 mg/kg/day) with no histopathologic correlate. Liver weight remained elevated following the recovery. The NOAEL was determined to be 1000 mg/kg/day (corresponding to an AUC value for avanafil of 85 μg·h/mL).
Finally, in the 26-week chronic toxicity study, decreased body weight and weight gain (1000 mg/kg/day), slight decreases in red blood cell parameters (1000 mg/kg/day), slight increases in white blood cell counts, reticulocytes, and alkaline phosphatase (1000 mg/kg/day), significant increases in liver weight (300 and 1000 mg/kg/day) and spleen weight (1000 mg/kg/day), centrilobular hepatocellular hypertrophy (300 and 1000 mg/kg/day), splenic extramedullary hematopoiesis (1000 mg/kg/day), and thyroid follicular cell hypertrophy (1000 mg/kg/day) were observed. With the exception of the red blood cell parameter changes, all of these effects resolved during recovery. The thyroid changes are likely a compensatory response to increased metabolism of thyroid hormones by the liver. The NOAEL is considered to be 300 mg/kg/day (corresponding to an AUC value for avanafil of 4.57 μg·h/mL in male rats; 9-times the unbound AUC at the MRHD).
In rats, as for mice, the liver was the primary target organ. In this organ as well as the spleen and thyroid, the effects are considered to be adaptive or compensatory and not adverse. The changes in ERGs were isolated (one-week study only) and not replicated in the chronic toxicity study.

Dogs were dosed orally with avanafil for one-week, two-weeks, 28 days and 9 months. Following one-week of dosing, clinical signs (100 mg/kg/day) were increased heart rate and slightly decreased blood pressure (10 mg/kg/day and above, not considered adverse at 10 or 30 mg/kg/day), increased liver weight (10 mg/kg/day and above), degeneration of the renal tubular epithelial cells (30 mg/kg/day), and arteritis in the coronary artery and arterioles of the epididymis (100 mg/kg/day) were noted in male beagle dogs. The NOAEL was considered to be 30 mg/kg/day (corresponding to an AUC value for avanafil of 62.5 μg·h/mL; 93-times the unbound AUC at the MRHD).
In a two-week study, beagle dogs exhibited sedation (100 mg/kg/day), decreased body weight and food consumption (100 mg/kg/day), increased heart rate and decreased blood pressure (100 mg/kg/day), and increased drug metabolizing enzyme activities (100 mg/kg/day). The NOAEL was considered to 30 mg/kg/day (corresponding to AUC values for avanafil of 29.8 and 41.6 μg·h/mL in males and females, respectively).
Administration of avanafil (in capsules) to male beagle dogs for 28 days produced toxicity (significant adverse clinical signs) at 100 mg/kg/day requiring a drug holiday and decrease in dose (75 mg/kg/day). Additionally, significantly decreased body weight and weight loss at 100/75 mg/kg/day, decreased thymus weight at 30 and 100/75 mg/kg/day, and lymphocytic depletion of the thymus at 30 and 100/75 mg/kg/day were observed. The NOEL was determined to be 10 mg/kg/day.
Chronic, 9-month (capsule) dosing to male beagle dogs produced decreased body weight (30 and 60 mg/kg/day). The NOAEL was 30 mg/kg/day (corresponding to an AUC value for avanafil of 24.1 μg·hr/mL; 36-times the unbound AUC at the MRHD).
Dogs exhibited cardiovascular effects (increased heart rate and decreased blood pressure) following administration of high doses of avanafil as well as effects on body weight, as were noted in the rodent species. Microscopic changes were only noted in the one-week and 28-day studies, and the organs and findings noted were not consistent and were not observed at the same doses administered for longer durations.

Relevance to human usage
In rodents the microscopic findings observed in the liver at high doses (hepatocellular hypertrophy) occur at higher levels of systemic exposure, as compared with the clinically relevant exposure. Increased liver enzymes have been uncommonly reported in clinical trials. The cardiovascular changes observed in dogs (decreased blood pressure and increased heart rate) represent pharmacodynamic effects which have been also recorded in clinical studies.

- Drug-Drug Interactions

  Avanafil at 10 and 100 µM was screened as inhibitor of an array of human transporters (expressed in host cells) which are known to play a role in DDI and/or in predicting drug toxicity (International Transporter Consortium, 2010; Hillgren et al, 2013).

  The only transporter that could be potentially affected by avanafil at clinically relevant concentrations is BCRP, however considering the clinical results obtained when co-administering avanafil at the MRHD and doxazosin (a substrate ofBCRP), the occurrence of effects indicative of higher plasma levels of the latter (but also of the former) drug due to an in vivo PK interaction can be reasonably excluded.
  Avanafil also inhibits BSEP (Ki of 9.52 µM) and this could have a potential impact on the liver. However, except the adaptive response to extensive hepatic metabolism observed following the administration of high doses in rodents, the analysis of non-clinical safety data, and clinical and post-marketing safety data do not provide any concern regarding liver toxicity in general, and DILI in particular, indicating that the inhibition of BSEP is not associated to these events because this effect is not obtained at clinically relevant concentrations, as the Ki of avanafil on BSEP is much greater than the unbound hepatic inlet concentration (0.32 µM).

  Relevance to human usage
  In conclusion, avanafil does not inhibit OATP1B1, OATP1B3, OCT, OCT2, OAT1, OAT3 and BSEP at clinically relevant concentrations. The inhibition exerted on BCRP is slightly below the threshold for triggering a DDI study with substrates of this transporter, but the analysis of the pharmacodynamic effects observed when avanafil was co-administered with a BCRP substrate would exclude that such an inhibition, if actually occurs at concentrations achieved at the MRHD, has a clinically relevant impact.

- Reproductive / developmental toxicity

  In a fertility and early embryonic development study, avanafil produced effects at the highest dose administered (1000 mg/kg/day); including a statistically significant increase in oestrous cycle length and a decrease in the mean number of oestrous cycles, a slight decrease in fertility, and a statistically significant decrease in sperm motility and increase in percentage of abnormal sperm (primarily detached sperm tails). The NOAEL for both parental toxicity as well as fertility and reproductive effects was 300 mg/kg/day (associated with an AUC value for avanafil of 4.57 µg·h/mL in males after 14-days; 9-times the unbound AUC at the MRHD). The AUCs for M4 and M16 at this dose were 14.3 and 0.904 µg·h/mL, respectively.
  A follow-up study evaluating reversibility of effects on fertility and sperm parameters has been conducted in male rats. There was no effect on fertility or pregnancy outcome

(uterine parameters) in females mated to avanafil treated males after 4 weeks of treatment. A decrease in sperm motility and increase in percentage of abnormal sperm were observed at the end of 9 weeks of treatment at 1000 mg/kg/day, but complete reversibility of sperm effects was seen in the avanafil treated males following the 9-week recovery period.
When avanafil was administered to pregnant rats (GD 6 to 17) at 1000 mg/kg/day, maternal toxicity (mortality, adverse clinical signs, decreased mean body weight, weight gain, and food consumption) and significantly decreased fetal body weight were observed. There was no increase in external, visceral or skeletal malformations or variations. The NOEL for maternal and developmental toxicity was 300 mg/kg/day (associated with a GD 17 AUC value for avanafil of 63.0 µg·h/mL; 121-times the unbound AUC at the MRHD. The AUCs for M4 and M16 at this dose were 8.47 and 1.40 µg·h/mL, respectively. Treatment of pregnant rabbits (GD 6 to 18) with 240 mg/kg/day produced maternal toxicity (decreased mean body weight and food consumption), but no effects on the fetus (body weight or the incidence of malformations or variations). The NOEL for maternal toxicity was 120 mg/kg/day and the NOEL for developmental toxicity was 240 mg/kg/day (associated with a GD 18 AUC value for avanafil of 45.7 µg·h/mL at 240 mg/kg/day; 39-times the unbound AUC at the MRHD). The AUCs for M4 and M16 at this dose were 16.5 and 54.4 µg·h/mL, respectively.
Exposure of pregnant rats through gestation and lactation produced maternal toxicity at 600 mg/kg/day (decrease in weight gain and food consumption) and effects on pup growth at 300 and 600 mg/kg/day (decreased body weight through the post-weaning period) with an associated delay in sexual maturation at 600 mg/kg/day (1060-035), but no other changes in the offspring (*e.g.*, development, sensory, reflexes, motor activity, learning and memory, reproduction, uterine parameters). The NOAEL was 300 mg/kg/day for P_0 maternal toxicity (associated with a GD 20 AUC value for avanafil of 139 µg·h/mL; 267-times the unbound AUC at the MRHD). The AUCs for M4 and M16 at this dose were 13.8 and 2.07 µg·h/mL, respectively. The NOEL for reproductive performance including parturition in the P_0 females was 600 mg/kg/day, the NOEL for behaviour and reproductive function in F_1 offspring was 600 mg/kg/day, and the NOEL for F_1 pup growth was 100 mg/kg/day.

Relevance to human usage
The target patient population of avanafil are males. The detrimental (but reversible) effect on rat semen is not of clinical concern since effect was only noted at very high doses (1000 mg/kg) with exposure margins >100-fold human AUC, and no effects were observed in dog semen analysis following 9-month treatment up to 60 mg/kg. Furthermore, the results from the clinical study TA-401 demonstrated that daily dosing with avanafil 100 mg for 26 weeks was generally well tolerated and was not associated with any untoward effects on sperm concentration, count, motility, or morphology.

- Genotoxicity

No evidence of genotoxic potential was found in *in vitro* tests of mutagenic potential in *Salmonella typhimurium* and *Escherichia coli* and there was no treatment related increase in chromosomal aberrations in studies using Chinese hamster CHL/IU cells and Chinese hamster ovary cells with and without metabolic activation. There was no increase in unscheduled DNA synthesis conducted in male rats subjected to single oral dose levels of up to 2000 mg/kg.

In the *in vitro* mouse lymphoma assay, avanafil was negative without metabolic activation with a 4-hour exposure period, equivocal without metabolic activation for a 24-hour exposure period, and positive with metabolic activation with a 4-hour exposure period. Importantly, avanafil was negative in the *in vivo* mouse micronucleus assay using i.p. doses of up to 1000 mg/kg.

Relevance to human usage
Not of clinical concern

- Carcinogenicity
  Avanafil was not carcinogenic in mice and rats when administered orally for two years at doses up to 600 and 1000 mg/kg/day, respectively.

  Relevance to human usage
  Not of clinical concern

Safety pharmacology

- Cardiovascular system, including potential effect on the QT interval

  Avanafil inhibits hERG current with an IC50 of 15 µM which represents a concentration approximately 416-fold above the clinically relevant unbound Cmax (~0.038 µM). Accordingly, avanafil did not modify the QT interval or other ECG parameters in conscious dogs up to a single dose of 30 mg/kg or 60 mg/kg for 39 weeks. At this dose, dogs showed increased heart rate and decreased blood pressure secondary to vasodilation.

  Relevance to human usage
  Expected pharmacological effect at high doses.

- Respiratory system

  Avanafil did not modify respiratory parameters in conscious dogs up to a single dose of 30 mg/kg.

  Relevance to human usage
  Not of clinical concern

- Central nervous system

  Avanafil decreased spontaneous locomotor activity in the mouse and rat at a high oral dose only (1000 mg/kg). Avanafil does not exhibit proconvulsant effects in mice up to the highest oral dose tested (300 mg/kg).

  Relevance to human usage
  Not of clinical concern

- Ocular effects

  Ocular effects are believed to be due to PDE6 inhibition, an off-target activity of PDE5 inhibitors. In the isolated rabbit retina study, avanafil increased the amplitude of b-waves at concentrations ≥ 3 μM which represents a concentration approximately 79-fold above the clinically relevant unbound Cmax (~0.038 μM). Avanafil had no effects on retinal response in anesthetized and conscious dogs (in contrast to sildenafil) up to single oral dose of 100 mg/kg (with a Cmax of 13.1 μg/mL, 50-fold above the unbound Cmax at the MRHD). In a 7-day repeat dose study in dogs, prolongation of a-wave latency (100 mg/kg/day) and slightly decreased ERG-wave amplitude ratios (30 and 100 mg/kg/day), however no such effects were noted following repeated doses up to 60 mg/kg for 39 weeks.

  Relevance to human usage
  At high doses PDE5 inhibitors can alter the vision by changing color perception, increased sensitivity to light and blurred vision.

Other toxicity-related information or data

Not available.

The non-clinical pharmacology, pharmacodynamics and toxicology of PDE5 inhibitors are well known. A comprehensive non-clinical program was conducted for avanafil that did not reveal any safety concerns that were previously unknown for the pharmacological class (e.g. cardiovascular effects secondary to vasodilatation) and all of these known class-related concerns were investigated in the clinical program for avanafil.
The non-clinical program did not include evaluation of immunotoxicity, juvenile animal toxicity, or local tolerance as these were not deemed necessary since there is no evidence of adverse effects on the immune system with PDE5 inhibitors, ED is a disease of older men and no paediatric use is envisaged, and avanafil is administered orally.
There are no special populations relevant to the use of avanafil in ED that would require additional non-clinical data.

PART II: MODULE SIII. - CLINICAL TRIAL EXPOSURE

Clinical development of avanafil (also referred to as TA-1790) was commenced by Mitsubishi Tanabe Pharma Corporation, which performed the first Phase I study (HP-01).
Development and commercial rights to the drug in North America, Europe and other territories were then licensed to VIVUS Inc.
VIVUS has conducted a comprehensive clinical development program to explore the efficacy and safety of avanafil as a treatment for ED. A total of 18 Phase I, 2 supportive Phase II, 1 pivotal Phase II and 3 pivotal Phase III clinical trials together with an open-label extension to two of the Phase III studies were presented in the Marketing Authorisation Application (MAA).
The Phase I program conducted in healthy subjects evaluated safety and pharmacokinetics of single and multiple oral doses of avanafil ranging from 12.5 mg to 800 mg, including the effect of food on pharmacokinetics (HP-01) (TA-02) (TA-07). A mass balance study was also conducted to further determine drug disposition and metabolites (TA-010). The effect of age on the pharmacokinetics of avanafil was explored (TA-014). A further study examined the effect of food, relative bioavailability and dose proportionality of two tablet formulations of avanafil intended for clinical trials and eventual marketing (TA-020). A study was also conducted to demonstrate dose equivalence of the three tablet strengths proposed for commercial use (TA-022). A specific study was conducted to evaluate the known effect with PDE5 inhibitors of low blood pressure when co-administered with a nitrate (TA-04). Given that avanafil is extensively metabolised via cytochrome P450 (CYP) 3A4, the effect of CYP3A4 inhibitors (ketoconazole, erythromycin, and ritonavir) on avanafil exposure were explored (TA-011). Further drug-drug interaction studies were performed with warfarin (TA-016 – this also included assessment of colour discrimination), desipramine, rosiglitazone and omeprazole (TA-018), and amlodipine (TA-019). Haemodynamic interactions between avanafil and alcohol (TA-015), doxasosin or tamsulosin (TA-017), enalapril or amlodipine (TA-019) were also explored. The effect of hepatic impairment (TA-012) and renal impairment (TA-013) on the pharmacokinetics of avanafil was examined. Another PDE5 inhibitor (tadalafil) has been associated with effects on spermatogenesis, therefore two studies were performed with avanafil examining spermatogenesis and sperm function (TA-014) (TA-021). Finally, the effect of avanafil on cardiac conduction was examined in a thorough QT study (TA-140).
Two Phase II studies were performed to examine the efficacy and safety of oral doses of avanafil in patients with ED. Dose levels used were those proposed for marketing – 50, 100, and 200 mg. The RigiScan™ monitor was used to assess penile rigidity in the first study (TA-01) and efficacy was measured via standard questionnaires in the second study (TA-03).
The pivotal clinical trial program consists of 4 placebo-controlled studies, all using standard subject questionnaires and a diary to assess efficacy. Oral doses of 50, 100 and 200 mg were administered. A Phase II dose ranging efficacy and safety study with doses between 50 mg and 300 mg was conducted in subjects with mild-moderate ED but without diabetes, spinal cord injury or following radical prostatectomy (TA-05). A Phase III study enrolled subjects with mild to severe ED but again excluded patients with diabetes, spinal cord injury or following radical prostatectomy (TA-301). However, one Phase III study did enroll subjects with mild to severe ED including those with Type 1 or 2 diabetes mellitus (TA-302) and the other enrolled subjects with mild to severe erectile dysfunction following bilateral nervesparing radical prostatectomy (TA-303).
The duration of subject participation in pivotal trials was limited to 12 weeks, during which time they could use avanafil on multiple occasions. However, longer term safety information was obtained from an open-label extension study for subjects completing TA-301 or TA-302

(TA-314). In this study, subjects could use avanafil 1 or 2 times per day (separated by at least 12 hours between doses) on multiple occasions for up to 12 months in the extension. In addition, dose titration, up or down, was allowed at the subject's request as determined by their response to treatment.
All the clinical trials were performed in accordance with applicable standards and to the principles and requirements of ICH Good Clinical Practice.

A total of 18 Phase I, two (2) supportive Phase II, one (1) pivotal Phase II, three (3) pivotal Phase III clinical trials, and a 1-year long-term extension study were conducted as part of the clinical development program for avanafil conducted by VIVUS, Inc. A total of 2144 subjects received at least one dose of avanafil with the maximum single dose being 800 mg.

To support the initial EU and US marketing authorisation applications, a total of 1500 subjects with ED received at least one dose of avanafil in the VIVUS-sponsored Phase II and III studies, including 201 subjects treated for up to a year in the long-term extension. The Phase III program included subjects in a generalised male population with ED, males with ED and with Type 1 or 2 diabetes mellitus, and males with ED following radical prostatectomy.

After marketing authorisation approval was received in the EU and US, VIVUS sponsored three (3) Phase IV studies. A total of 440 subjects with ED were randomised in the interventional Phase IV study TA-501, conducted by VIVUS, Inc. A total of 295 of the subjects received at least one dose of avanafil. The main objective of this Phase IV study was to examine the therapeutic effects of two doses of avanafil (100 mg and 200 mg) approximately 15 minutes after dosing in men with mild to severe ED.

A total of 80 subjects aged 18 to 45 years of age inclusive were randomised in the Phase IV study TA-402. The objectives of this study were to assess the effect of 200 mg avanafil on visual acuity, pupillometry, colour vision discrimination, and intraocular pressure (IOP) in healthy male subjects. 40 subjects received 200 mg avanafil (2 x 100 mg tablets) and 40 subjects received matching placebo tablets.

A total of 181 subjects were randomised in the Phase IV study TA-401 and 90 received treatment with avanafil. The primary objective of this clinical trial is to assess the effect of daily treatment with avanafil 100 mg on spermatogenesis over a period of 26 weeks in healthy male subjects. The secondary objective is to evaluate the safety and tolerability of daily use of avanafil in these subjects.

In addition to the VIVUS-sponsored studies, JW PHARMA sponsored a Phase III study JW-AVA-302 to assess the efficacy and safety of 100 mg and 200 mg of avanafil compared to placebo in patients with moderate to severe ED. A total of 195 Korean subjects were randomised in two (2) groups: 130 subjects in the avanafil group and 65 subjects in the placebo group. In the avanafil group, 24 subjects took only avanafil 100 mg and 106 subjects took avanafil 100 mg for four (4) weeks and avanafil 200 mg for eight (8) weeks.
A Phase III clinical trial registration trial was conducted by Sanofi in Russia (AVANAL07163). There were 189 patients enrolled in three (3) groups (63 patients in each group of avanafil 100 mg, avanafil 200 mg, and placebo).
A Phase I clinical trial, conducted by Menarini (AVAN-OG) in which 49 subjects received avanafil 200 mg oral granules with water, 200 mg oral granules without water, and an avanafil 200 mg tablet over three (3) separate study sessions.
Table S III–1.1: Estimated subject exposure from completed clinical trials

Treatment	Number of subjects
Avanafil	2863
Placebo	1257

Source: Clinical Study Reports for HP-01, TA-02, TA-04, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, TA-140, TA-01, TA-03, TA-05, TA-301, TA-302, TA-303, TA-314, TA-501, TA-401, TA-402 and JW-AVA-302, AVANAL07163 and AVAN-OG.

Subject exposure to investigational drug from completed clinical trials by age group (Table SIII-1-2) and breakdown by elderly age group (Table SIII-1-3).

Table S III–1.2: Subject exposure to investigational drug from completed clinical trials by age group*

Age group	Persons
18 to ≤65 years	2342
>65 years	397

Source: HP-01, TA-01, TA-02, TA-03, TA-04, TA-05, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, TA-140, TA-301, TA-302, TA-303, TA-314, TA-401, TA-402, TA-501, JW-AVA-302 and AVAN-OG

Table S III–1.3: Subject exposure to investigational drug from completed clinical trials breakdown by elderly age group

Breakdown by elderly age group					
	Age 65-69 n/N (%)	**Age 70-74 n/N (%)**	**Age 75-79 n/N (%)**	**Age 80-84 n/N (%)**	**Age ≥ 85 n/N (%)**
PK*/Special Populations/ DDI**/Safety[1]	11/680 (1.6%)	14/680 (2.1%)	7/680 (1.0%)	1/680 (0.1%)	0/680 (0.0%)
Controlled Trials[2]	256/1763 (15.7%)	83/1763 (5.1%)	28/1763 (1.7%)	2/1763 (0.1%)	1/1763 (0.1%)
Non-Controlled trials[3]	95/712 (13.3%)	44/712 (6.2%)	22/712 (3.1%)	1/712 (0.1%)	1/712 (0.1%)

[1] Includes data from HP-01, TA-02, TA-04, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, and TA-140. Numerator includes subjects from studies TA-12, TA-13, and TA-14.
[2] Controlled trials include TA-01, TA-03, TA-05, TA-301, TA-302, and TA-303.
[3] Non-controlled trials include TA-314. Subjects who received placebo in studies TA-301 and TA-302 received avanafil in study TA-314.
n=number of subjects in the age range; N=total number of subjects; %=n/N.
* PK = pharmacokinetics
** DDI = drug-drug interactions
Sources: HP-01, TA-01, TA-02, TA-03, TA-04, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, and TA-140 CSRs, and Post-Analysis

Table S III–1.4: Subject exposure to investigational drug from completed clinical trials by number of separate doses taken

Number of separate doses taken (Indication: Erectile dysfunction)		
No. Doses	**Persons**	**Person Time (persons x months)**
1 dose	321	N/A

2 to 4 doses	381	N/A
4 to 10 doses	347	N/A
>10 doses	1193	N/A

Source: HP-01, TA-01, TA-02, TA-03, TA-04, TA-05, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, TA-140, TA-301, TA-302, TA-303, and TA-314 and AVAN-OG.

Table S III–1.5: Subject exposure to investigational drug from completed clinical trials by ethnic origin.

Ethnic origin **(Indication: Erectile dysfunction))**	
Ethnic group	**Persons**
White/Caucasian	1513
Black/Afro-American	283
Asian	1
Other	49
Total	1846

Source: Efficacy and safety studies only TA-01, TA-03, TA-05, TA-301, TA-302, TA-303, TA-501, TA-401 and TA-402 and AVAN-OG

Table S III–1.6: Subject exposure to investigational drug from completed clinical trials in special populations

Special populations **(Indication: Erectile dysfunction)**		
Special population	**Persons**	**Person Time**
Renal impairment	16	Single dose
Mild	8	Single dose
Moderate	8	Single dose
Severe	0	
Hepatic impairment	16	Single dose
Mild	8	Single dose
Moderate	8	Single dose
Severe	0	
Type 1 or 2 Diabetes Mellitus	301	N/A
Radical Prostatectomy	190	N/A

N/A = not available

PART II: MODULE SIV. - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Patients excluded from the clinical development program of avanafil were those with a history of hypersensitivity to avanafil or other PDE5 inhibitors or a known history of dose-limiting adverse effects with another PDE5 inhibitor, patients with significant cardiovascular disease (stoke, myocardial infarction, life-threatening arrhythmia) within the past 6 months, or a history of heart failure, unstable angina requiring treatment. Patients with hepatic or severe renal impairment were excluded as were patients with retinitis pigmentosa. Penile lesions or deformities were also an exclusion criterion as was treatment with a nitrate or CYP3A4 inhibitor.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Adult Males with Pre-existing overt and covert Cardiovascular Disease

Reason for exclusion:
Clinical trial protocols specifically excluded subjects with significant cardiovascular disease such as previous stroke, myocardial infarction, life-threatening arrhythmia, heart failure, unstable angina pectoris, or uncontrolled hypertension. This is common practice for pre-authorisation clinical trials of PDE5 inhibitors as this group present a risk of cardiovascular side effects not only due to the potentially negative impact of PDE5-induced vasodilatation in the presence of acute or severe chronic cardiovascular disease states but also because sexual activity itself in such men may be regarded as clinically inadvisable.

Additionally, patients with left ventricular outflow tract 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.

Is it considered to be included as missing information?
No

Rationale:
Use by adult males with pre-existing overt and covert cardiovascular disease is contraindicated in the SmPC.

Adult Males with Severe Renal or Hepatic impairment

Reason for exclusion:
Standard exclusion criteria in clinical trials.

Is it considered to be included as missing information?
No.

Rationale:
Use of avanafil in adult males with severe renal or hepatic impairment is contraindicated in the SmPC.

Patients with Retinitis Pigmentosa

Reason for exclusion:

It is unknown if inhibition of PDE6 by PDE5 inhibitors is likely to exacerbate abnormal cGMP metabolism within the photoreceptor cells of individuals with retinitis pigmentosa.

Is it considered to be included as missing information?
No.

Rationale
Use of avanafil in patients with retinitis pigmentosa is contraindicated in the proposed SmPC.

Very Elderly Males >70 years

Reason for exclusion:
The mean age of adult males included in the clinical development program was approximately 56 years with 13.5% of patients being >65 years. In later pivotal trials (TA-301, TA-302) and in the long-term extension to these trials (TA-314) a few males into their 80's were exposed to avanafil. However, there is a relative lack of safety information in the very elderly (defined here as >70 years) age group in the clinical program.

The prevalence of ED increases with increasing age, yet the desire to engage in sexual activity by the very elderly male may remain. Therefore, it is likely that men who are >70 years of age will be treated with avanafil. Although safety data in this age group is lacking, the overall safety of PDE5 inhibitors as a pharmacological class is well defined both via clinical development data for other products and many years of marketing of other PDE5 inhibitors. Also, there was no evidence in the avanafil clinical development program for side effects unique to the drug nor an increase frequency of side effects in the adult males studied compared to other PDE5 inhibitors. This is consistent with the high selectivity of avanafil for the PDE5 receptor.

Is it considered to be included as missing information?
No.

Rationale
There is no reason to suspect that the side effect profile of avanafil will be different in males >70 years compared to the population studied.

Adults Males with ED Due to Spinal Cord injury

Reason for exclusion:
ED is a potential consequence of spinal cord injury. It is uncommon for patients with spinal cord injury to be enrolled in pre-registration clinical trials of a PDE5 inhibitor due to the practical difficulties of following-up this sub-group of patients. Reports of clinical trials are available in the literature that demonstrates the effectiveness of PDE5 inhibitors in this sub-group.

Is it considered to be included as missing information?
No.

Rationale

There is no reason to suspect that the safety of avanafil will be different than in the general population with ED.

Patients with bleeding disorders or active peptic ulceration

Reason for exclusion:
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.

Is it considered to be included as missing information?
No.

Rationale
There is no reason to suspect that the safety of avanafil will be different than in the general population with ED.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect ADRs with a very rare frequency (< 1 / 10,000). ADRs with a frequency greater than 1 in 954 (one third of the overall population exposed to Avanafil in the clinical development) could be detected if there were no background incidence.

The Avanafil administration in all studies was carried out for short periods, and in the only study conducted for a time of 52 weeks (TA-314) it was administrered with an intermittent use. TEAEs were reported in 275 (38.7%) of patients and 79 (11.1%) of subjects had a TEAE considered as related to avanafil by the investigator. The majority of TEAEs were mild or moderate in severity. There were no deaths and only 11 (1.5%) of subjects reported an SAE, none of which were regarded as related to avanafil by the investigator. Only 20 (2.8%) of patients discontinued the study due to a TEAE. For 10 (1.4%) subjects, the adverse event that led to discontinuation was considered by the investigator to be related to study drug. Compared to the baseline results at study entry, there were no clinically relevant changes over 52 weeks in vital signs, laboratory parameters or ECGs. Thus, there was regular exposure to avanafil during the study that likely represents postmarketing exposure. Accordingly, the lack of any new safety signals in this long-term study is reassuring.

No long term follow-up was performed. Therefore, no data are available.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table S IV–1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment	A total of 16 patients with history of hepatic impairment were exposed to avanafil.
Patients with relevant comorbidities: • Patients with renal impairment	A total of 16 patients with history of renal impairment were exposed to avanafil. as creatinine clearance < 90 mL/min.
Patients with relevant comorbidities: • Patients with cardiovascular impairment	Not included in the clinical development program.
Patients with relevant comorbidities: • Immuno-compromised patients • Patients with a disease severity different from inclusion criteria in clinical trials.	Not included in the clinical development program
Population with relevant different ethnic origin	A total of 1,513 patients included in the clinical development program were white/caucasian, 283 patients were black/afro-american, one was asian. Other 49 patients were classified as other ethnic origin. (Source: Efficacy and safety studies only TA-01, TA-03, TA-05, TA-301, TA-302, TA-303, TA-501, TA-401 TA-402 and AVAN-OG)
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other: • Patients < 18 years of age	Not included in the clinical development program
Other: • Patients >65 years of age	A total of 397 elderly patients were included in the clinical development program (Source: HP-01, TA-01, TA-02, TA-03, TA-04, TA-05, TA-07, TA-010, TA-011, TA-012, TA-013, TA-014, TA-015, TA-016, TA-017, TA-018, TA-019, TA-020, TA-021, TA-022, TA-140, TA-301, TA-302, TA-303, TA-314, TA-401, TA-402, TA-501,JW-AVA-302 and AVAN-OG)

PART II: MODULE SV. - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure
Post-authorisation interval exposure for Europe, USA and South Korea has been calculated on the basis of internal sales data. A therapeutic cycle is defined as a patient taking one (1) tablet of avanafil in any strength.

SV.1.2 Exposure
Based on the above assumption, the cumulative post-marketing exposure to all strengths of avanafil up through May-2024 is 44,422,345 therapeutic cycles.

Table SV–1: Cumulative (from Launch through May-2024) Exposure of Avanafil (Number of Therapeutic Cycles) in Europe by Country and Dose, Data from MENARINI

Country	Launch date	50 mg	100 mg	200 mg	Total
Austria	May-2014	30,508	205,370	245,860	481,738
Belgium	May-2014	153,388	1,138,684	1,223,776	2,515,848
Bulgaria	Jun-2014	11,260	48,708	10,664	70,632
Croatia	Apr-2014	3,820	30,740	104,752	139,312
Cyprus	Oct-2015	3,648	13,166	22,804	39,618
Czech Republic	Apr-2014	10,220	189,926	359,876	560,022
Denmark	Aug-2014	1,652	3,724	1,092	6,468
Estonia	Jun-2014	9,232	57,960	84,624	151,816
Finland	Jul-2014	10,180	67,520	65,528	143,228
France	Mar-2014	327,020	3,692,550	3,786,392	7,805,962
Germany	Mar-2014	116,828	619,856	579,800	1,316,484
Greece	Apr-2015	46,784	221,312	224,912	493,008
Hungary	May-2014	4,848	96,664	216,288	317,800
Ireland	Jun-2014	10,432	41,328	29,516	81,276
Italy	Mar-2014	745,320	6,959,856	6,072,292	13,777,468
Latvia	Jun-2014	2,232	45,404	69,324	116,960
Lithuania	Jun-2014	13,236	245,628	341,092	599,956
Luxembourg	May-2014	11,840	141,752	209,272	362,864
Malta	Feb-2015	7,776	40,800	17,472	66,048
Netherlands	May-2014	23,512	50,392	53,608	127,512

Country	Launch date	50 mg	100 mg	200 mg	Total
Poland	Apr-2014	23,372	193,620	181,180	398,172
Portugal	Sep-2014	128,692	1,084,344	561,000	1,774,036
Romania	Jun-2014	45,740	337,020	37,012	419,772
Slovakia	May-2014	4,016	40,636	35,912	80,564
Slovenia	Jun-2014	1,904	51,620	73,308	126,832
Spain	Apr-2014	498,952	2,454,802	1,528,848	4,482,602
Switzerland	Jan-2016	14,268	86,824	230,460	331,552
UK	Mar-2014	264,900	1,174,260	920,624	2,359,784
Total Europe		**2,525,580**	**19,334,466**	**17,287,288**	**39,147,334**

Abbreviations: UK=United Kingdom

Table SV–2: Cumulative (Dec-2013 – Jun-2024) Exposure of Avanafil (Number of Therapeutic Cycles) in US by Dose, Data from MIST (until 26-Jun-2020) and Metuchen (from Apr-2020 to Jun-2024)

Country	50 mg	100 mg	200 mg	Total
US	938,182	1,913,761	539,410	3,391,353

Abbreviations: US=United States

Table SV–3: Cumulative (Nov-2011- Jun-2023*) Exposure of Avanafil (Number of Therapeutic Cycles) in South Korea by Dose, Data from JW PHARMA

Country	100 mg	200 mg	Total
South Korea	43,323	975,989	1,019,312

*Data available only until Jun 2023

Table SV–4: Cumulative (to May-2024) exposure of avanafil (number of Therapeutic Cycles) in Hong Kong by Dose, Data from MENARINI

Country	Launch date	50 mg	100 mg	200 mg	Total
Hong Kong	Aug-2017	0	1,884	69,080	70,964

Table SV–5: Cumulative (to May-2024) Exposure of Avanafil (Number of Therapeutic Cycles) in Australia by Dose, Data from MENARINI

Country	Launch date	50 mg	100 mg	200 mg	Total
Australia	Jan-2019	31,008	160,008	344,584	535,600

Table SV–6: Cumulative (to May-2024) Exposure of Avanafil (Number of Therapeutic Cycles) in Singapore by Dose, Data from MENARINI

Country	Launch date	50 mg	100 mg	200 mg	Total
Singapore	Sep-2020	0	0	86,744	86,744

Table SV–7: Cumulative (to May-2024) exposure of avanafil (number of Therapeutic Cycles) in Taiwan by Dose, Data from MENARINI

Country	Launch date	50 mg	100 mg	200 mg	Total
Taiwan	Nov-2021	0	0	167,984	167,984

Table SV–8: Cumulative (Sep-2015 to Jun-2024*) Exposure of Avanafil (Number of Therapeutic Cycles) by Country and Dose, Data from Sanofi-Aventis

Country	50 mg	100 mg	200 mg	Total
Saudia Arabia	240	240	240	720
Jordan	60	100	100	260
Lebanon	8	8	8	24
Nigeria	630	630	630	1,890
United Arab Emirates	0	40	120	160
Total	**938**	**1,018**	**1,098**	**3,054**

*The sales data are available from Sep-2015 to Oct-2016 only

PART II: MODULE SVI. - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes is considered to be low for avanafil. There are reports of recreational use and misuse of other PDE5 inhibitors in social settings by young adult males, mainly restricted to the most well-known brand name of sildenafil. For the majority of such use, the primary concern would be the incidence of nuisance side effects such as headache, though more serious side effects such as priapism are more likely in a younger population. There is some evidence for abuse of PDE5 inhibitors by subjects with chronic medical conditions that may be contraindicated in the proposed SmPC for avanafil, and in subjects with HIV. Recreational abuse of a PDE5 inhibitor may be in conjunction with other illicit drugs such as ketamine or, more seriously amyl nitrate (which in combination with a PDE5 inhibitor may cause profound hypotension).

PART II: MODULE SVII. - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

As described in the guidance on the format of the risk management plan (RMP) in EU – in integrated format rev 2.0.1 dated October 2018, this section is expected to be submitted only for initial marketing authorization applications.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP
As described in the guidance on the format of the risk management plan (RMP) in EU – in integrated format rev 2.0.1 dated October 2018, this section is expected to be submitted only for initial marketing authorization applications.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

As described in the guidance on the format of the risk management plan (RMP) in EU – in integrated format rev 2.0.1 dated October 2018, this section is expected to be submitted only for initial marketing authorization applications.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

RMP version 6.0 (current) vs RMP version 5.1

- “Cardiovascular risk in patients with pre-existing overt and covert cardiovascular disease” and “Prolonged erection (priapism)” previously classified as important identified risks, have been removed from the list of safety concerns.
- “Hypotension/increased hypotensive effect”, “Non-arteritic anterior ischaemic optic neuropathy” and “Sudden hearing loss” previously classified as potential risks, have been removed from the list of safety concerns.
- “Very elderly males > 70 years of age”, “Use in subject with severe renal or hepatic failure”, “Adults males with ED due to spinal cord injury”, “Patients with retinitis pigmentosa” and “Patients with bleeding disorders or active peptic ulceration” previously classified as missing information, have been removed from the list of safety concerns.

The safety concerns list has been revised according the the PRAC recommendation received in the context of the latest two PSUSA procedures (EMEA/H/C/PSUSA/00010066/202006 and EMEA/H/C/PSUSA/00010066/202306) in which the MAH was requested to update the RMP according to the GVP Module V on Risk Management Systems rev 2. Since neither additional pharmacovigilance activities nor additional risk minimisation measures are in place, the list of safety concerns in the RMP has been updated and the proposed list is currently empty.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

None.

SVII.3.2 Presentation of the missing information

None.

PART II: MODULE SVIII. - SUMMARY OF THE SAFETY CONCERNS

The present section of the RMP corresponds to a summary of the safety concerns identified for avanafil products in previous Module SVII of Part II. Such information is given in tabular format sorted as: important identified risks, important potential risks and missing information.

Table S VIII–1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III. : PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The present Pharmacovigilance Plan provides details of the pharmacovigilance activities to be applied to the concerned products by reviewing each safety concern of the product as noted in Part II SVIII (Summary of the safety concerns) of the present RMP as well as to identify new ones (signal detection).

III.1. ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered adequate for the safety monitoring of the product.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- Specific adverse reaction follow-up questionnaires for safety concerns:
  Not applicable.
  No specific adverse reaction follow-up questionnaires are in place.

- Other forms of routine pharmacovigilance activities:
  Not applicable.
  A review of the safety concerns will be performed at each PSUR elaboration.

III.2. ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.
No additional activities are actually ongoing.
No additional pharmacovigilance activities are planned for the concerned products.

III.3. SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table Part III–1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV. : PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.
There are no ongoing or planned imposed post-authorisation efficacy studies concerned avanafil containing products.

PART V. : RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. ROUTINE RISK MINIMISATION MEASURES

Table Part V–1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
None	Not applicable

V.2. ADDITIONAL RISK MINIMISATION MEASURES

Not applicable. No important identified risk, important potential risk and missing information are included in the safety concerns list (Part II: Module SVIII).

V.3. SUMMARY OF RISK MINIMISATION MEASURES

Table Part V–3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
None	Not applicable	Not applicable

PART VI. : SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR SPEDRA (AVANAFIL)

This is a summary of the risk management plan (RMP) for Spedra. The RMP details important risks of Spedra, how these risks can be minimised, and how more information will be obtained about Spedra's risks and uncertainties (missing information).
Spedra's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Spedra should be used.

This summary of the RMP for Spedra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Spedra's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Spedra is authorised for the treatment of erectile dysfunction in adult men (see SmPC for the full indication). It contains avanafil as the active substance and it is given by oral (50 mg, 100 mg and 200 mg tablets) administration.

Further information about the evaluation of Spedra’s benefits can be found in Spedra’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/spedra.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Spedra, together with measures to minimise such risks and the proposed studies for learning more about Spedra's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of important risks and missing information

Important risks of Spedra are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered or taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Spedra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B. Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risk, potential risk or Missing information: None	
Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	Not applicable
Risk minimisation measures	Not applicable

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation
There are no studies which are conditions of the marketing authorisation of specific obligation of Spedra.

II.C.2. Other studies in post-authorisation development plan
There are no studies required for Spedra.

PART VII. : ANNEXES

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

Not applicable.