Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Avanafil

Proprietary Product Name: Spedra

Sponsor: A.Menarini Australia Pty Ltd

October 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the drug concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve from time zero to the time of the last measurable concentration
$AUC_{0\text{-}tau}$	Area under the drug concentration-time curve over the dosing interval
$AUEC_{0\text{-}t}$	Area under the effect-time curve from time 0 to time t
BID	Twice daily
BMI	Body mass index
cGMP	Cyclic guanosine monophosphate
CL_{int}	Intrinsic metabolic clearance
C_{max}	Maximum observed plasma drug concentration
$C_{max,ss}$	Maximum observed plasma drug concentration at steady-state
CSR	Clinical Study Report
DAE	Discontinuation due to adverse event
DBP	Diastolic blood pressure
EAS	Erection Assessment Scale
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation	Meaning
ED	Erectile dysfunction
EF	Erectile function
EOT	End of treatment
FDA	US Food and Drug Administration
GCP	Good clinical practices
HbA1c	Haemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IC_{50}	Half maximal inhibitory concentration
IIEF	International Index of Erectile Function
INR	International normalized ratio
ITT	Intent to treat
IVRS	Interactive voice response system
LOCF	Last observation carried forward
LS	Least squares
MDCK-WT	Madin-Darby canine kidney wild type
MDR1	Multi-drug resistance gene
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OTC	Over the counter
Papp	Apparent permeability
PD	Pharmacodynamic
PDE5	Phosphodiesterase 5
Pgp	P-glycoprotein
PK	Pharmacokinetic
PT	Prothrombin time
QD	Once daily

Abbreviation	Meaning
QTcB	Bazett-corrected QT
QTcF	Fridericia-corrected QT
QtcI	Individual-corrected QT
RE	Efflux ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SEP	Sexual Encounter Profile
SOC	System organ class
TEAE	Treatment-emergent adverse event t½ Terminal elimination half-life
T_{max}	Time to reach the maximum plasma concentration
VSS	Visual sexual stimulation

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	10 November 2015
Date of entry onto ARTG	6 April 2016
Active ingredient(s):	Avanafil
Product name(s):	Spedra
Sponsor's name and address:	A.Menarini Australia Pty Ltd
Dose form(s):	Uncoated tablets
Strength(s):	50, 100 and 200 mg
Container(s):	Poly-Vinyl-Chloride (PVC)/poly-chloro-tri-fluoro-ethylene (PCTFE) film and aluminium lidding foil
Pack size(s):	1 (sample pack), 2, 4, 8 or 12 tablets
Approved therapeutic use:	*Treatment of erectile dysfunction in adult males*.
Route(s) of administration:	Oral
Dosage:	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).
ARTG number (s):	228476, 228475, 228474

Product background

This AusPAR describes the application by the sponsor, A.Menarini Australia Pty Ltd, to register a new chemical entity Avanafil (as Spedra) for the following indication

Treatment of erectile dysfunction in men.

Spedra is intended for use prior to anticipated sexual activity and sexual stimulation is required for a response to treatment. The proposed dose is 100 mg taken as needed at least 15 minutes before sexual activity. Spedra can be taken with or without food.

Based on individual efficacy and tolerability, the sponsor proposed that the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum proposed dosing frequency is once per day.

Avanafil is a highly selective and potent, 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.

The sponsor states that '*Avanafil is a new PDE5 inhibitor for oral administration and was developed for its high selectivity for the PDE5 isoenzyme relative to other PDE5 inhibitors. Avanafil is rapidly absorbed following administration, reaching peak plasma concentration between 30 to 45 minutes in the fasted state giving the opportunity for clinical effectiveness as early as 15 minutes after administration*.'

Currently registered pharmaceutical treatments for erectile dysfunction include three other PDE5 inhibitors (sildenafil, tadalafil and vardenafil) and alprostadil.

There are no specific European Union (EU) guidelines adopted by the TGA relevant to this submission, besides the general guidelines which include the QT guideline[1].

Regulatory status

Spedra is a new chemical entity for Australian regulatory purposes. Avanafil has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM).

Avanafil has been approved in the EU (June 2013), USA (April 2012) and New Zealand (January 2015) with applications pending in Canada The approved indications in the USA, EU New Zealand and Switzerland are as follows:

- USA:

  Stendra is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction.

- EU:

  Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required

[1] ICH Topic E 14 Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

- Switzerland:

  Treatment of erectile dysfunction in adult men. In order for Spedra to be effective, sexual stimulation is required

- New Zealand:

  Spedra is indicated as a treatment of erectile function in adult men. In order for Spedra to be effective, sexual stimulation is required.

Product Information

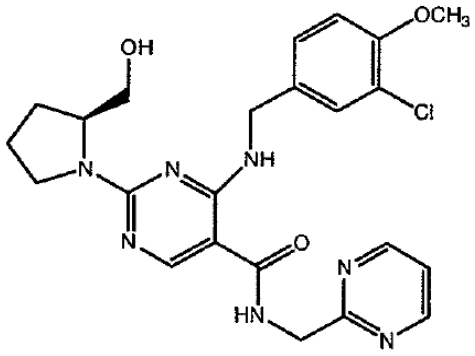
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

The chemical name of avanafil is (S)-4-(3-Chloro-4-methoxybenzylamino)-2-(2-hydroxymethylpyrrolidin-1-yl)-N-pyrimidin-2-ylmethyl-5-pyrimidinecarboxamide and has the following structural formula (Figure 1):

Figure 1: Chemical structure of avanafil



Avanafil is a white crystal or white crystalline powder, slightly soluble in methanol and ethanol and practically insoluble in water. Avanafil has only one crystalline form, therefore no polymorphism was observed. The structure of avanafil was supported by elemental analysis, InfraRed (IR), UltraViolet (UV), 1 hydrogen (1H) and 13 carbon (13C) Nuclear Magnetic Resonance Spectroscopy (NMR), mass spectrometry (MS) and X-ray diffraction (XRD).

The active pharmaceutical ingredient (API) is considered to be in BCS Class[2] II (low solubility, high permeability). The solubility of the API is pH dependant; it exhibits higher solubility in more acidic conditions. Despite the API's poor solubility, control of particle size distribution was not considered to be a Critical Quality Attribute (CQA) as the finished product was formulated with fumaric acid, creating an acidic microenvironment for the drug, resulting in very rapid dissolution.

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Avanafil exhibits stereoisomerism due to the presence of 1 chiral centre and exists as the S conformer. The stereochemical configuration was determined by XRD.

Avanafil is synthesised chemically using commercially available starting materials.

The active substance is manufactured by one manufacturer.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential impurities were well discussed with regards to their origin and characterised.

The levels of the impurities were supported by the results of toxicological studies and appropriate specification limits have been set.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The API specification includes tests for description, identification (IR, High Performance Liquid Chromatography (HPLC)), assay (HPLC), purity (HPLC), residual solvents (chromatography(GC)), heavy metals (European Pharmacopeia (Ph Eur)), palladium (Inductively coupled plasma mass spectrometry (ICP-MS)), optical isomer (HPLC), reagent (GC) and residue on ignition.

Batch analysis data of 9 commercial scale batches of the API were provided. The results were within the specifications and consistent from batch to batch.

Three production scale batches of the API packed in the intended commercial package (double polyethylene bags which are individually sealed with plastic ties and placed into fibre drums closed with metal lids with security pegs) from the proposed manufacturer were put on stability testing as per International Conference on Harmonisation (ICH) conditions: under long term for 18 months, and accelerated for up 6 months for three batches. Photostability test following ICH guidelines Q1B[3] was performed on one batch. Results on stress conditions during 3 months were also provided on one batch. Avanafil was investigated under conditions prepared with water, acidic and basis reagents, and hydrogen peroxide.

The following parameters were tested: description, purity, optical isomer, loss of drying and assay.

The stability studies have proven that avanafil is mostly sensitive to oxidative conditions and to light exposure when it is in the liquid state.

Stability results showed that the API manufactured by the proposed supplier is very stable. The stability results justify the proposed retest period in the proposed container.

Drug product

The finished product was developed as an immediate release, oral tablet formulation because a rapid onset of efficacy was desired.

Although the solubility of avanafil is high under acidic conditions, it is very low in the neutral to alkali pH. Thus, a highly water soluble organic acid was desired as a solubilising agent to improve the solubility of the active substance. Fumaric acid was specifically chosen because it exhibited the best compatibility with the active substance of the agents tested. The optimal ratio of fumaric acid to avanafil resulting in tablets with acceptable properties (weight, thickness and hardness) and dissolution characteristics was determined in a formulation study. Active granules

[3]ICH Guideline: Stability Testing: Photostability Testing of New Drug Substances and Products Q1B.

(avanafil/mannitol/hydroxypropylcellulose) were prepared with different particle sizes of the active substance.

Using the aforementioned active granules, the method for addition of the fumaric acid was determined in a study as a part of manufacturing process development.

In order to accelerate the disintegration and dissolution of the tablets in an acidic environment (for example, the stomach) the effect of adding precipitated calcium carbonate was studied. The formulation with precipitated calcium carbonate disintegrated faster than that without precipitated calcium carbonate in all test medium because of the bubbling effect between acid and base. From this study, the optimal amount of calcium carbonate that resulted in rapid disintegration of avanafil tablets without significantly raising the pH was determined. Therefore, precipitated calcium carbonate was included in the avanafil tablet formulation.

Compatibility with conventional immediate release excipients were evaluated by preliminary stability studies. All of the chosen excipients were compatible with the active substance under the tested storage conditions. Compatibility has also been confirmed by the results of stability studies of the finished product.

The CQAs of the immediate-release Avanafil tablets are dissolution rate and dose uniformity. A set of experiments was conducted to elucidate the Critical Process Parameters (CPPs) for the Avanafil tablet manufacturing process. Control ranges have been established for these parameters to assure reproducibility of the CQAs of the product.

Two formulations (Formulation I and II) were used in clinical studies during the Avanafil Tablet development program. Both formulations have identical excipients (with the exception of the colorant added to Formulation II). The formulation used in Phase III clinical studies (Formulation II) is the proposed formulation for the commercial product. A clinical bioequivalence study was performed to compare Formulation I and Formulation II, and bioequivalence between the two formulations were demonstrated.

The primary packaging proposed is PVC/PCTFE/Aluminium foil blisters. The material complies with Ph Eur (discussed below in *Biopharmaceutics*) requirements and it is adequate to support the stability and use of the product.

The manufacturing process consists of 6 main steps: milling, preparation of binder solutions, formation of active granules, formation of fumaric acid granules, blending and tableting.

The process is considered to be a standard manufacturing process. Therefore, the absence of process validation data on commercial scale batches in the dossier is considered acceptable. The applicant submitted the validation scheme and the commitment to perform process validation at commercial scale (3 consecutive batches) prior to placing the medicinal product on the market for two strengths (100 mg and 200 mg). With regard to the 50 mg strength a concurrent validation was applied for. The Annex 15 to the EU Guide to Good Manufacturing Practice states that in particular circumstances it may be possible to validate a process during routine production (concurrent validation). In this case, considering that the granule is the same for the different strengths (50 mg, 100 mg and 200 mg) and that only one batch of the 50 mg strength will be manufactured per year, the proposal was considered acceptable

The finished product release specifications include appropriate tests for description, identification (IR, HPLC), assay (HPLC), purity (HPLC), uniformity of dosage unit (Ph Eur), dissolution (Ph Eur), Total Aerobic Microbial Count (Ph Eur), Total Combined Yeast and Mould Count (Ph Eur) and Escherichia coli (Ph Eur).

Batch analysis results in 3 pilot scale batches per strength confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability data of 9 pilot scale batches, three of each dose strength (50 mg, 100 mg and 200 mg), packaged in the proposed commercial packaging configuration stored under long term conditions for 18 to 24 months and for up to 12 months under both intermediate conditions and accelerate conditions according to ICH guidelines were provided. The pilot batches used are identical to those proposed for marketing and were packed in the same primary packaging proposed for marketing.

Samples were tested for description (appearance), identification (HPLC), assay (HPLC), purity (HPLC), dissolution (Ph Eur), total aerobic microbial count (Ph Eur), total combined yeast and mould count (Ph Eur). The analytical procedures used were stability indicating.

In addition, three batches (one of each dose strength) were exposed to stress conditions and were exposed to light as defined in the ICH Guideline Q1B[3] to assess the stability of the product when exposed directly to conditions of high temperature.

Based on available stability data, the proposed shelf-life of 4 years 'Store below 25°C' is acceptable.

Biopharmaceutics

Formulation I versus Formulation II

Two avanafil immediate release (IR) tablet formulations were used during its clinical development: Formulation I and Formulation II. Both formulations contained the same set of excipients (mannitol, fumaric acid, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, calcium carbonate, and magnesium stearate) in the same relative ratios. The two formulations differed in two ways: (1) Formulation II contained a higher ratio of avanafil active pharmaceutical ingredient (API) to total excipient weight than did Formulation I, and (2) Formulation II incorporated the addition of a trace colorant. Formulation I (12.5, 25, 50 and 100 mg tablet strengths) was an early avanafil tablet formulation containing the API and the excipient weight in a 1:2 ratio. Formulation II (50, 100 and 200 mg tablet strengths) is the proposed commercial formulation and contains the API and the excipient weight in a 1:1 ratio. A bioequivalence study was conducted, in part, to assess the bioavailability of the two avanafil formulations. The study was conducted using healthy volunteers in the fasted state. The results demonstrate that the two formulations are bioequivalent with respect to both peak plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC).

Food effect

Food effect was also studied in two separate studies. The TA-020 study was a Phase I, single-centre, open-label, randomised and four period crossover study to assess the effect of food on the pharmacokinetics of avanafil. Subjects receiving treatment with food began eating a standardised high fat breakfast 30 ± 5 minutes prior to dosing. Standard meals were provided uniformly to all subjects at approximately 4 and 9 h after dosing, and an evening snack was provided approximately 12 to 13 h after dosing. Blood samples for the determination of plasma avanafil and its metabolite concentrations were obtained from each subject at 0 (30 minutes pre dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 8, 12, 18, and 24 h post dose in each treatment period. The absence of a food effect was concluded if the corresponding 90% confidence intervals (CIs) for the ratios of the geometric least squares (LS) Means of Treatment B (2 x 100 mg tablet fed) to Treatment A (2 x 100 mg tablet fasted) were contained within the equivalence range of 80% to 125% for each of the parameters. The statistical comparison of avanafil C_{max} for Treatment B (2 x 100 mg tablet fed) versus Treatment A (2 x 100 mg tablet fasted) showed that the 90% CIs of the geometric LS Means ratio was outside the 80% to 125% range. The % mean ratio of

avanafil untransformed C_{max} of 61.00% suggested that mean maximum avanafil exposure was lower following avanafil administered under fed versus fasted conditions. A significant difference between time to C_{max} (T_{max}) for test and reference was observed. The median T_{max} was approximately 1.27 h longer under fed conditions.

The other study that investigated the food effect on the pharmacokinetics of avanafil after a high fat meal was Study HP-01. Avanafil was given to 6 volunteers who received 100 mg avanafil under fasting and fed conditions. Absorption of avanafil was delayed in the presence of food with T_{max} observed between 1.25 and 4 h compared to 0.25 to 1.25 h in the fasting state. C_{max} decreased by 24%. This effect is supported by the 90 % confidence intervals (0.56 to 0.97) which are outside the (0.80 to 1.25) range. Conversely, food increased the mean AUC from time 0 to time t (AUC_{0-t}) and AUC from time 0 to infinity (AUC_{0-inf}) by the 25 % and 14 % respectively. This increase is supported by the 90 % confidence intervals, which are respectively (1.10 to 1.39) and (0.90 to 1.45). Mean terminal half-life (t½) of avanafil is lower after food intake (about 9 h) than in the fasted state (about 17 h). However, high mean value of t½ in the fasted state can be mostly attributed to the high t½ (49 h) of one subject. When comparing the corresponding median values, which are more suitable for the comparison between two treatments, it turns that the observed differences are weak (12 h versus 10 h). In conclusion, the C_{max} values were approximately 39% lower under fed conditions and the median T_{max} was delayed from less than 1 h in fasted conditions to 2 h (range 1.2 to 4h) after food intake.

The *Dosage and Administration* section of the PI states the drug can be taken without regards to meals. The *Pharmacokinetics* section of the PI states that *'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 h and a mean reduction in C_{max} of 39% (200 mg)'*.

The information provided in relation to food intake appears to be appropriate as the later stage clinical efficacy trials were carried out without regard to meals. The information in the pharmacokinetic section should be amended to include a statement alerting prescribers to individualise their patients' dosing relative to their food intake based on their own experienced clinical response. A statement such as that included in the sildenafil PI *'Patients may need to individualise their dosing relative to their food intake based on their own experienced clinical response'* is appropriate. Furthermore, the paragraph structure under the *Pharmacokinetics* section of the PI should be amended as follows:

> *'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 Tmax of 1.25 h and a mean reduction in Cmax of 39% (200 mg). The small changes in avanafil Cmax 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.'*

Pharmacokinetics – Linearity

The Study HP-01 *'A double-blind, ascending single oral dose, safety tolerability and PK study of TA 1790 in healthy male volunteers'* was a single centre (Paris) 8 ascending dose (12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg and 800 mg) in parallel groups in healthy male volunteers. Seven groups received the doses fasting and the 100 mg group had 2 periods dosed first in the fasted state and second in fed state (high fat meal). The study enrolled 65 subjects (age 18 to 35 years old) and 64 subjects completed the study. Forty eight were used for pharmacokinetic analysis. Blood sampling was at the initial (0),

0.25, 0.5, 0.75, 1.25, 1.5, 2, 3, 4, 6, 8, 12 and 24 h time points post dose. Dose normalised log-transformed C_{max} were not significantly different from 12.5 to 600 mg, while AUC was not significantly different over the entire dose range. The increase was proportional for C_{max} up to 600 mg and for the entire range for AUC up to 800 mg.

The *Pharmacokinetics* section of the PI states that *'The pharmacokinetics of avanafil are dose proportional over the recommended dose range'*.

Given the results of Study HP-01 and that the recommended dose range is 50 to 200 mg daily, this statement is considered to be acceptable.

Dose proportionality

This Phase I single centre, open label, randomised, three period crossover study was designed to assess the dose equivalence of three dose strengths of avanafil tablets (Formulation II) 50, 100, and 200 mg in healthy male subjects. Each eligible subject was randomised to receive the following three treatments in a three-way crossover fashion:

Treatment A: 4 x 50 mg Formulation II avanafil tablets

Treatment B: 2 x 100 mg Formulation II avanafil tablets

Treatment C: 1 x 200 mg Formulation II avanafil tablet

Following oral administration, avanafil was rapidly absorbed with a median T_{max} of 0.50 to 0.75 h in the fasted state. The statistical comparisons of avanafil C_{max}, AUC_{0-t}, and AUC_{0-inf} between Treatment C (1 x 200 mg) versus Treatment A (4 x 50 mg) showed that the 90% CIs of the geometric LS mean ratios were within the 80% to 125% range. The statistical comparisons of avanafil C_{max}, AUC_{0-t}, and AUC_{0-inf} for Treatment C (1 x 200 mg) versus Treatment B (2 x 100 mg) showed that the 90% CIs of the geometric LS mean ratios were within the 80% to 125% range. These results indicate that the 200 mg dose strength is dose equivalent with the 50 mg and 100 mg dose strengths.

Quality summary and conclusions

Provided that the changes to the Quality and Biopharmaceutic aspects of the PI noted above are made, registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical data were compliant with the relevant ICH guidelines, and all pivotal safety studies were conducted under Good Laboratory Conditions (GLP) conditions.

Pharmacology

Primary pharmacology

Avanafil inhibited PDE5 from canine lung with a 50% inhibitory concentration (IC_{50}) of 4.2 to 5.2 nM, and from human platelets with an IC_{50} of 8.9 nM. The inhibitory activity is similar to, or moderately lower than, other PDE5 inhibitors (IC_{50}: sildenafil 1.6 nM in canine lung and 4.3 nM in human platelets; vardenafil 0.08 nM; tadalafil 4.0 nM). The avanafil metabolites M4, M16 and M27 were weak inhibitors of PDE5 (IC_{50} values of 51,

4100 and 4500 nM, respectively). Based on the relative activity in human platelets, and taking into account plasma levels and protein binding, M4 was estimated to contribute approximately 12% of the pharmacological activity of avanafil. Due to the modest contribution to pharmacological activity the exposure to M4 was not included in the calculation of exposure ratios. Avanafil was a weak inhibitor of PDE6 with an IC_{50} of 630 nM. Inhibition of other PDE isoenzymes by avanafil all occurred with IC_{50} values ≥ 5700 nM.

In vitro, ≥10 nM avanafil dose-dependently induced and augmented electrical field stimulation-induced relaxation in isolated corpus cavernosum from New Zealand White (NZW) rabbits. In vivo, intravenous administration of avanafil dose dependently potentiated penile tumescence in NZW rabbits, mongrel dogs and cynomolgus monkeys. Intraduodenal administration to dogs also potentiated penile tumescence in dogs, with a 200% effective dose (ED_{200}) of 152 µg/kg which was higher than the ED_{200} for intravenous (IV) administration (38 µg/kg). The plasma concentrations of avanafil at the ED_{200} were estimated to be 60 and 25 ng/mL following IV and intraduodenal administration, respectively. Following intraduodenal administration, peak penile tumescence response was observed 10 and 30 minutes post-dose for avanafil and sildenafil, respectively.

Secondary pharmacodynamics and safety pharmacology

Secondary pharmacodynamic pharmacology studies indicated that avanafil did not affect nitric oxide synthase activity and is not an adenosine receptor antagonist. In addition, avanafil did not affect radioligand binding to 17 other receptors and ion channels.

Specialised safety pharmacology studies covered the cardiovascular, respiratory, ocular, central nervous system (CNS), renal and gastrointestinal systems, as well as assessing effects on coagulation and fibrinolysis. Key cardiovascular (in vitro hERG K^+ channel and isolated Purkinje fibre studies, in vivo beagle dog study), CNS and ocular safety studies were conducted under GLP conditions. The expected class effects were observed, including decreased blood pressure and increased heart rate. Avanafil inhibited hERG channels with an IC_{50} of 16 µM, which is >350 times the unbound C_{max} observed in men that received the maximum recommended human dose (MRHD) of 200 mg. Modest (≤41%) inhibition of sodium channels (hHNa) and L-type calcium channels was also observed with avanafil at concentrations ≤50 µM but IC_{50} values were not calculated. In isolated Purkinje fibres, 1 to100 µM avanafil decreased action potential duration to 60% repolarisation (APD_{60}) and to 90% (APD_{90}) by up to 11%, suggesting that the net effect of hERG, hHNa and L-type calcium channel inhibition would not lead to QT prolongation[4]. In conscious beagle dogs, there were no adverse effects of avanafil on ECG parameters. Avanafil had similar or less potent vasorelaxation properties as sildenafil in rat aorta with endothelium intact or denuded. Intravenous infusion of avanafil in anesthetised dogs decreased mean arterial pressure at doses ≥ 1 µg/kg/min, while ≥10 mg/kg PO avanafil decreased blood pressure in conscious beagle dogs. The effects of avanafil on blood pressure, heart rate and haemodynamics were generally milder compared to the effects of sildenafil. There was no effect of avanafil on the respiratory system.

Electroretinography (ERG) assessment in isolated rabbit retina found ≥3 µM avanafil increased b- wave amplitude, and a- and b- wave implicit time. However, in conscious and anaesthetised dogs there was no effect of avanafil on ERG parameters. This is in contrast to sildenafil which altered ERG waveform and increased latency.

[4] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.

Avanafil had minimal effect on the CNS system following a single dose. A modest decrease in spontaneous locomotor activity was observed in rodents that received 1000 mg/kg avanafil. In addition, there was a non-significant trend for ≥100 mg/kg avanafil to increase pentobarbital induced sleep time. Avanafil did not affect body temperature or have any analgesic effects. Similarly, avanafil did not have pro or anticonvulsant activity but the test systems in which these were assessed did not include positive controls to validate their sensitivity. Following repeated oral administration of high avanafil doses, adverse CNS effects including hypoactivity, tremors and ataxia were observed in rats (≥ 1000 mg/kg/day) and dogs (≥ 75mg/kg/day). Relative animal:human exposures (compared to the exposure expected in humans) at these doses were >127 based on unbound AUC.

Renal function appeared to be transiently decreased by ≥ 10 mg/kg avanafil. Urinary volume as well as sodium and chloride excretion were decreased from 0 to 5 h post dose, but were no different over 0 to 24 h. The urinary sodium to potassium ratio was also decreased from both 0 to 5 and 0 to 24 h. In the pivotal rat repeat dose study, urinary volume was dose dependently increased, but with no other changes in the urinalysis.

Avanafil (10 µM) decreased spasmogen induced contractions in isolated guinea pig ileum and decreased the amplitude of contraction in isolated rabbit jejunum. These effects occurred at concentrations lower than the predicted concentration of avanafil in the intestine. However, in mice, avanafil had no effect on gastric emptying or small intestinal transit. In rats, 300 mg/kg avanafil decreased gastric fluid and gastric acid secretion (relative animal:human exposure ≥17 based on AUC in males in the repeat dose study).

Avanafil had no direct effect on collagen induced platelet aggregation but potentiated the inhibitory effects of sodium nitroprusside on platelet aggregation but to a lesser extent than sildenafil. Based on unbound C_{max}, this effect is not anticipated to occur clinically. In rats there was no effect of daily dosing of avanafil (≤ 300 mg/kg/day for 5 days) on coagulation or fibrinolysis parameters.

Avanafil enhanced the hypotensive effect of nitroglycerin in mongrel dogs that received 0.1 and 1 mg/kg intraduodenally. These dose levels are associated with exposure ratios of 0.02 and 0.2 based on mg/m^2, respectively. Therefore, interactions between nitroglycerin and avanafil are likely to occur at clinical exposures.

Pharmacokinetics

Absorption

Oral doses of avanafil were rapidly absorbed with T_{max} values of 0.5 to 1h in humans and rodents and approximately 1 to 6 h in dogs. T_{max} was delayed in laboratory animals that received high doses of avanafil. There was no consistent effect of repeated dosing on pharmacokinetic parameters. In male dogs, T_{max}, C_{max} and AUC values were increased in fed compared to fasted animals. Exposure to avanafil was dose proportional in mice, rats and dogs. Oral bioavailability was reduced by extensive first pass metabolism, with bioavailability very low in rats (1.5%), moderate in dogs (30 to 40%) and low in monkeys (15%). Exposure in female rats was markedly higher than in male rats but there was no consistent effect of gender in mice, and gender differences were not investigated in dogs. The plasma half-life of avanafil was short in rats (0.2 to 3 h; 12.7 h at high dose of 2000 mg/kg PO), dogs (0.6 to 2), monkeys (0.3 to 0.8 h) and humans (1.1 to 1.5 h).

Distribution

Avanafil was highly bound to human plasma proteins (99%), in particular albumin. Plasma protein binding was lower in laboratory animals: approximately 91% in rats, 96% in rabbits and 93% in dogs. Similar to the parent drug, the plasma protein binding of the

major human metabolites M4 and M16 was higher in humans than laboratory animals, with binding of M4 higher than M16 (97% and 80-84%, respectively, in humans). There was no specific distribution of avanafil into red blood cells in humans or laboratory animals. Tissue distribution of avanafil and/or its metabolites was wide and rapid, with highest levels of radioactivity observed in liver, kidney and adrenal glands. Only low levels of radioactivity were observed in the brain, spinal cord and testes, indicating minimal penetration of the blood-brain and blood-testis barrier. Binding to melanin was indicated by retention of avanafil in pigmented tissues in rats, with radioactivity still present in the uveal tract seven days after dosing. Compared to sildenafil, the retention of avanafil in the eye was approximately two fold lower in terms of AUC and half-life.

Metabolism

Avanafil was extensively metabolised in male rats, with moderate metabolism in male dogs and male humans (plasma unchanged drug 17%, 56 to 70% and 37%, respectively). Two major metabolites were identified in humans that were formed by hydroxylation (M4) and oxidative cleavage to open the pyrrolidine ring (M16). Twenty four other metabolites were identified, formed by hydroxylation, oxidation, *N*-dealkylation, demethylation, dehydrogenation and glucuronide conjugation, or a combination of these processes. The plasma metabolites identified in humans were also observed in rats and dogs but two minor metabolites (≤ 2.5%) identified in human urine and faeces were not observed in laboratory animals (M30 and M31). As these metabolites were not observed in plasma, and were present at levels <10% they do not require nonclinical characterisation.[5] Cytochrome P450 (CYP) 3A4 was identified as the major avanafil metabolising CYP isoform, with CYP2C also contributing to the formation of the demethylated metabolite (M2) in vitro.

Avanafil inhibited a number of CYP isoforms (2C8, 2C9, 2C19, 2D6 and 3A4) in vitro but as the inhibitor constant (Ki) values were much greater than anticipated clinical exposure this is unlikely to cause in vivo inhibition either systemically or within the gut. Similarly, avanafil metabolites M4 and M16 modestly inhibited CYP1A and 2A6 at concentrations ≥10 μM, but inhibition is unlikely to occur with therapeutic doses as unbound C_{max} was <0.3 μM for both metabolites. Treatment of human hepatocytes with 50 μM avanafil led to a modest induction of CYP2B6 and minimal induction of CYP1A2 and CYP3A4. CYP induction is unlikely clinically given the high avanafil concentration required to induce these enzymes. In repeat dose studies, aniline hydroxylase was induced in livers of rats and dogs that received ≥100 mg/kg/day orally (PO) (relative animal:human exposure to humans: 2.4 in male rats and >100 in dogs based on AUC).

Excretion

Avanafil was excreted predominantly via the biliary/faecal route in rats, dogs, monkeys and humans. Moderate urinary excretion was observed in cynomolgus monkeys and humans (11 to 24%) compared to beagle dogs and SD rats (< 8.3%). A major role of biliary excretion was demonstrated in SD rats, with enterohepatic circulation evident.

Conclusion

Similar pharmacokinetic profiles were observed in laboratory animals and humans, with the exception of plasma protein binding, which was higher in humans. While oral bioavailability was very low in rats, adequate exposures to avanafil and its major metabolites (M4 and M16) were achieved in the toxicity studies. Therefore, the studies

[5] ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. EMA/CPMP/ICH/286/1995

conducted in rats and dogs are suitable for assessing the toxicity of avanafil, but the difference in plasma protein binding should be considered in calculating relative animal:human exposures.

Pharmacokinetic drug interactions

Avanafil was a weak substrate for P-glycoprotein (P-gp), but not (Cancer Resistance Protein) BCRP. Based on the ratio of efflux ratios in MDR1 and wild type MDCK cells, avanafil did not inhibit P-glycoprotein transport of digoxin. However, only one concentration of avanafil was used (10 μM). The predicted intestinal concentration of avanafil is 1.65 mM[6]. Therefore, it is unclear whether avanafil may inhibit intestinal P-glycoprotein. However, rapid absorption of avanafil suggests that this potential interaction could be managed clinically.

Avanafil did not inhibit organic cation transporter type 2 (OCT2) but did inhibit BCRP, Bile Salt Export Pump (BSEP), organic anion transporting polypeptides (OATP1) subtypes B1 and B3, OCT1 and OAT3. Inhibition of OATP1B3, OCT1 and OAT3 was <50% with 10 μM avanafil and is therefore unlikely to occur in vivo as the unbound C_{max} was 0.05 μM following repeated dosing at the MRHD. Similarly, while IC_{50} and or Ki values were not calculated for BSEP and OATP1B1, the inhibition by 10 μM avanafil was 59%, and therefore unlikely to occur with therapeutic dosing. Avanafil inhibited BCRP with an IC_{50} of 1.4 μM and estimated K_i value of 1.1 μM. It is expected that avanafil would inhibit intestinal BCRP. However, as for P-gp this inhibition could be managed clinically given the rapid absorption of avanafil. Systemic inhibition of BCRP is not expected to occur clinically as the unbound C_{max} for avanafil was 0.05 μM at the MRHD.

Toxicology

Acute toxicity

In rodents, doses of ≤ 2000 mg/kg PO and ≤40 mg/kg IV were well tolerated with no mortality and minimal clinical signs observed. Similarly, oral doses of ≤ 2000 mg/kg were also well tolerated in dogs but the post-dose observation phase was shorter than the standard 14 day period used in the rodent studies. Overall, the data indicate that avanafil has low toxicity by the clinical (oral) route.

Repeat-dose toxicity

Repeat-dose studies of oral avanafil administration were conducted in CD-1 mice[7] (13 weeks), Sprague-Dawley (SD) rats (1, 2, 4 and 26 weeks) and beagle dogs (1, 2, 4 week and 9 months). In rodents, full toxicokinetic data were collected from bridging studies which used the same dosing regimens for shorter durations. Pivotal studies were generally conducted in accordance with ICH guidelines. However, the dog study used only male animals. As the proposed indication for avanafil is for use only in males, this is not considered a deficiency.

Relative animal:human exposure

Exposure ratios have been calculated based on animal: human plasma AUC_{0-24h}. For rat and dog studies the exposure ratio was calculated using unbound drug but for the mouse study total drug was used as plasma protein binding was not measured in mice. The

[6] Calculated as dose/250 mL, based on guidance in EMA guideline: CPMP/EWP/560/95/Rev. 1 Corr.* *Guideline on the Investigation of Drug Interactions.*
[7] Outbred stocks Charles River Breeding Laboratories

maximum dose in mice was 2000 (decreased to 1000) mg/kg/day PO, in rats was 1000 mg/kg/day PO and in dogs was 60 mg/kg/day PO. The data from shorter term studies was used to estimate exposure ratios. In all studies, high safety margins were achieved, with higher exposure observed in female animals. A high relative animal: human exposure to the weakly pharmacologically active M4 metabolite was also demonstrated in male rats.

Table I. Relative animal: human exposure in repeat-dose toxicity and carcinogenicity studies

Species	Study duration (study ID)	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)		Exposure ratio#	
			♂	♀	♂	♀
Avanafil						
Mouse (CD-1)	13 weeks (6584-150*)	200	5510	14,600	1.3	3.5
		600	88,100	80,200	21.4	19.5
		2000→1000	64,300	142,200	15.6	34.6
Rat (SD)	26 weeks (6584-149 / 10-AVANAFIL-TOX-08^)	100	1115	12,353	2.4	27
		300	7619	99,203	17	217
		1000	64,791	269,380	142	589
Dog (Beagle, ♂)	9 months (6584-142)	10	5850		10	
		30	24,070		41	
		60	74,400		127	
Human (healthy ♂ volunteers)	steady state (TA-02)	200 mg	4113		–	
M4 (active metabolite)						
Rat (SD)	2 weeks (1060-048)	300	14,300	–	54	–
		1000	218,000	–	821	–
Human (healthy ♂	steady state (TA-012)	200 mg	2170		–	

Species	Study duration (study ID)	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
volunteers)				

= animal:human plasma AUC_{0-24h}, corrected for plasma protein binding for rat and dog studies;
*Toxicokinetics not performed in 2 year study; ^Only limited toxicokinetic data were collected during the 26 week study (1h and 24h plasma avanafil levels). A separate 2 week toxicokinetic study was conducted to estimate exposure, but only male rats were used and only the mid- and high-dose levels administered. Therefore, exposure ratios were calculated using the toxicokinetic data from Study 10-AVANAFIL-TOX-08, a 2 week study conducted in male and female rats using the same dosing regimen.

Major toxicities

The major target organs for avanafil were the liver, thyroid, heart, kidney and adrenal gland which are consistent with the target organs of other PDE5 inhibitors. In addition, red and white blood cell parameters were affected by avanafil.

In rats that received 1000 mg/kg/day PO avanafil (relative animal: human exposure ≥142) for 26 weeks there was a modest decrease in erythrocytes and haemoglobin, and an increase in mean corpuscular volume. In addition, reticulocyte numbers tended to be increased. The decrease in erythrocyte numbers and increase in cell volume was not reversed after a 4 week recovery. Lymphocyte numbers were also increased in this group of rats but these changes were reversible. Similarly, there was a modest increase in mean corpuscular volume and haemoglobin, and also a trend for increased reticulocytes in dogs that received 60 mg/kg/day PO avanafil for 9 months (relative animal:human exposure 127 compared to humans). The modest sizes of the changes in haematology parameters, together with the high relative animal:human exposures, indicate that these effects are unlikely to be clinically relevant.

The observed class effects included:

- Increased liver weight in rats that received ≥300 mg/kg/day PO (relative animal: human exposure 17 in males and 217 in females), associated with hepatocellular hypertrophy. Liver weight also showed a trend to increase dogs that received ≥10 mg/kg/day PO for 9 months.
- The incidence of thyroid hypertrophy was increased in rats that received 1000 mg/kg/day PO avanafil. This is a common observation associated with induction of liver enzyme leading to increased clearance of thyroid hormone. An increased incidence in thyroid and parathyroid cysts was also observed in dogs, but it is unclear if this is a class effect.
- Vascular inflammation was observed in the heart of one of five dogs that received 60 mg/kg/day avanafil for 9 months. In addition, arteritis was observed in the heart and testis in one of two dogs that received 100 mg/kg/day for one week. Arteritis was also reported in dog repeat dose studies of sildenafil and tadalafil. In the 2 year mouse carcinogenicity study there was an increased incidence of thrombus in the heart of mice that received 600 mg/kg/day, but this was not observed in long term studies in rats (2 years) and dogs (9 months).
- Kidney weight was increased in rats that received ≥ 300 mg/kg/day avanafil for 26 weeks, but there were no microscopic correlates. Increased kidney weight was also observed in repeat-dose toxicity studies of vardenafil. In dogs, only mild effects of avanafil were observed in the kidney, with a modest increase in tubular mineralisation and tubular epithelium regeneration.
- Adrenal gland weight was increased in all groups in the pivotal rat (≥100 mg/kg/day PO) and dog (≥10 mg/kg/day) studies, without microscopic correlates. Increased adrenal gland weight has also been reported in studies of vardenafil and sildenafil, and is thought to be secondary to haemodynamic changes.

In summary, no new target organs were identified for avanafil in comparison to the known class effects of PDE5 inhibitors. The toxicities observed were generally mild and only occurred with high exposure ratios. Given that the proposed indication in humans is for intermittent use, the pivotal studies indicate minimal toxicological concerns.

Genotoxicity

Genotoxicity was assessed in a standard battery of tests. Studies were GLP compliant and conducted according to ICH guideline S2 (R1)[8]. The in vitro tests included two bacterial reverse mutagenesis assays, two mammalian chromosomal aberration assays and one mouse lymphoma L5178Y cell TK gene mutation assay. All were negative, except the mouse lymphoma cell assay, which was positive after 4h in cells incubated with an activated S9 mix[9]. Genotoxicity was also assessed in mice that received 500 to 2000 mg/kg avanafil in a micronucleus assay and a study of unscheduled deoxyribonucleic acid (DNA) synthesis in liver cells. The results of both studies were negative. Overall, the weight of evidence indicates a low genotoxic potential for avanafil as the isolated positive result in the mouse lymphoma assay is offset by the negative results in the rest of the genotoxicity battery of tests including the in vivo micronucleus study.

Carcinogenicity

The carcinogenicity studies conducted in rodents were consistent with ICH guideline S1B[10]. Both studies were conducted under guidance from the FDA Executive Carcinogenicity Assessment Committee (CAC), including advice on dose selection. The high dose in mice was 600 mg/kg, giving an exposure ratio of approximately 16 in males and 35 in females based on total AUC. In rats, the high dose of 1000 mg/kg was associated with exposure ratios of 142 in males and 589 in females based on unbound AUC. However, it should be noted the exposure estimates were taken from separate studies at earlier time points, and in mice used a different vehicle. Therefore the exposure ratios should be considered as approximations only.

In mice, there was an increased incidence of hepatocellular carcinomas (malignant) but this was not statistically significant. Similarly, in rats there was an increase in the incidence of hepatocellular adenomas (benign). The FDA Executive CAC review concluded these findings were not significant, and that there were no treatment-related neoplasms in the mouse or rat study. Together with the high estimated exposure ratios the studies indicate a low carcinogenic potential for avanafil.

Reproductive toxicity

Reproductive toxicity studies that addressed ICH guideline S5(R2)[11] were conducted in rats and rabbits. Two fertility studies were conducted in rats, with the first study treating males and females with 100 to 1000 mg/kg/day PO avanafil, and the second treating males only with 1000 mg/kg/day PO avanafil. The duration of avanafil administration was 2 or 4 weeks prior to mating for females and males respectively. In the embryofetal development studies, avanafil was administered during the period of organogenesis to pregnant rats (gestational day (GD) 6 to GD17) and rabbits (GD6 to GD18). A pre- post-natal study was conducted in rats in which dams received 100 to 600 mg/kg/day PO avanafil from the beginning of organogenesis until weaning (GD6 to lactation day (LD) 20).

[8] Guidance for Industry: S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use
[9] The S9 fraction is the product of an organ tissue homogenate used in biological assays. The S9 fraction is most frequently used in assays that measure the metabolism of drugs and other xenobiotics.
[10] ICH harmonised tripartite guideline: Testing for carcinogenicity of pharmaceuticals S1B
[11] ICH Topic S 5 (R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

Selected offspring were evaluated for growth, behaviour, sexual maturation and reproductive performance. All studies were conducted under GLP conditions, and utilised study designs that met ICH guidance in terms of treatment durations and timing, species and group sizes.

Relative animal:human exposure

The relative animal:human exposure in animals compared to humans are summarised in Table 2 below.

Table 2: Relative animal:human exposure in reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Unbound exposure ratio[#]
Rat (SD)	Embryofetal development (1060-048*)	100	10,200	22
		300	63,000	138
	Pre- post- natal study (160-048*)	100	14,000	31
		300	139,000	304
		600	199,000	435
Rabbit (NZW)	Embryofetal development (160-049)	120	18,600	18
		240	45,700	44
Human (healthy ♂ volunteers)	steady state	200 mg	4113	–

[#] = animal:human plasma AUC_{0-24h} corrected for plasma protein binding which was 99% in humans, 91% in rats and 96% in rabbits; *Toxicokinetic data taken from a bridging study which administered avanafil to pregnant rats from GD6-GD17 using the same formulation as the embryofetal study (0.5% carboxymethylcellulose, 0.1% hydrogenated castor oil-60) but only in the low and mid-dose groups, and from GD6-GD20 using the same formulation as the pre- post-natal study (0.5% carboxymethylcellulose, 0.1% Cremophor® RH40)

Relative animal: human exposures were determined in bridging studies and not in the reproductive toxicity studies and therefore should be considered estimates. Relative animal: human exposure for the fertility studies can be approximated from the exposures in rats presented in Table 1. High relative animal:human exposures were achieved in the reproductive toxicity studies. It should be noted that exposure data was not available for rabbits that received 30 or 60 mg/kg/day in the embryofetal development study. Placental transfer and excretion in milk were not assessed, which is not considered a deficiency given the proposed indication is for use only in males.

Maternal toxicity, characterised by decreased body weight, food intake and mortality (1/25), was observed in females that received 1000 mg/kg/day PO avanafil (relative animal: human exposure 589). In these females, estrus cycle length increased from 4.5 to 5.6 days, and there was a 16% decrease in number of pregnant rats. Pre-implantation losses also tended to increase in dams that received the high dose (6.3% in controls, 10.3% at the high dose (HD)). The No observable adverse effect level (NOAEL) for female fertility was 300 mg/kg/day PO (relative animal: human exposure 217). Paternal toxicity (decreased body weight), decreased sperm motility (no motility in some individuals) and

an increased proportion of abnormal sperm were observed in males that received 1000 mg/kg/day PO avanafil (relative animal: human exposure 142). Despite these changes, there was no adverse effect of fertility or pregnancy outcomes including fertility and fecundity indices or pre-implantation losses. Based on the adverse effects on sperm the NOAEL for male fertility was 300 mg/kg/day PO (relative animal: human exposure 17). The effects on sperm motility and morphology were shown to be reversible following a 9 week recovery period.

In the rat embryofetal development study there was marked maternal toxicity in the high dose group with mortality in 6 of 25 dams that received 1000 mg/kg/day PO (relative animal:human exposure >138, based on exposure in 300 mg/kg/day group which received same formulation). In the surviving dams, weight gain was also decreased. Maternal toxicity was associated with reduced pup weight. Malformations of the aortic arch and innominate artery were observed in one pup from a dam that received 1000 mg/kg/day but there were no other treatment-related abnormalities.

In rabbits, ≥240 mg/kg/day avanafil was associated with maternal weight loss and decreased food intake but weight was regained after cessation of treatment. There was a significant increase in late resorptions in does that received 240 mg/kg, with the rate of 0.7% exceeding the historical control range of 0 to 0.4%. In does that received ≥60 mg/kg/day avanafil there was a dose-dependent increase in the incidence of an extra subclavian artery. This variation was not reported in the historical controls and is therefore considered to be treatment-related. There were no other treatment-related effects on the incidence of variations or malformations observed. One pup from a HD doe had severe malformations including anencephaly, misshapen, fused or absent skull bones and extra thoracic vertebrae at the neural arch. The majority of these or similar malformations were observed at low incidence in the historical control data and therefore these effects are likely to be spontaneous as they were confined to a single fetus.

Overall, the weight of data from the embryofetal development studies does not indicate that avanafil is teratogenic. In rats, the NOAEL for embryofetal development was 300 mg/kg/day PO (relative animal: human exposure 138 based on free AUC) based on maternal toxicity and reduced pup weight at the higher dose. In rabbits, the NOAEL for embryofetal development was 30 mg/kg/day PO (relative animal:human exposure 7, based on mg/m^2) due to the treatment-related incidence on an extra subclavian artery.

In the pre and postnatal study 100 to 600 mg/kg/day PO avanafil was administered from GD6 to LD20. Body weight was decreased in the offspring of dams that received 600 mg/kg/day and remained significantly lower throughout the study. Sexual maturation was delayed in female offspring of HD dams and also tended to be delayed in males. However, body weights and age at sexual maturation remained in the historical control range. Similarly, body weight was reduced in the offspring of dams that received 300 mg/kg/day PO avanafil at weaning (Day 21) and post-weaning (Day 28) but weights remained in the historical control range. There were no significant effects of avanafil on behaviour or reproductive performance in F1 pups. A brain malformation was observed in one female F1 pup from a HD dam but the relationship to treatment is unclear. In addition, hydrocephaly was observed in one pup from a low dose (LD) dam and one from a HD dam at the post-weaning necroscopy. However, hydrocephaly was reported in the historical control data for embryofetal toxicity studies and therefore this observation was not considered treatment-related.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1[12]. Based on the findings in the rabbit embryofetal development study a Pregnancy Category of B3[13] is recommended.

Phototoxicity

The phototoxicity of avanafil was assessed in pigmented rats. The assay was validated by using a positive phototoxic control (8-Methoxypsoralen), which is consistent with ICH guideline S10.[3] There was no evidence of either ocular or skin phototoxicity in male rats that received ≤1000 mg/kg PO avanafil.

Impurities

The proposed specification for a process-related impurity in the drug substance has been adequately qualified.

Nonclinical summary

- The nonclinical data were of high quality and adequately addressed the relevant ICH guidelines. All pivotal safety studies were conducted under GLP conditions.
- Avanafil inhibits phosphodiesterase type 5 (PDE5) with an IC_{50} of 4 to 9 nM, which is similar to other PDE5 inhibitors (sildenafil, tadalafil, vardenafil). Avanafil was also a weak inhibitor of PDE6 with an IC_{50} of 630 nM but showed little inhibition of other PDE isoforms (IC_{50} values ≥5700 nM). The major metabolites also showed weak inhibition of PDE5, with IC_{50} values of 51 and 4100 nM for metabolites M4 and M16, respectively. The M4 metabolite was estimated to contribute to approximately 12% of the pharmacological activity of avanafil.
- In vitro, avanafil induced and augmented relaxation in isolated rabbit corpus cavernosum tissue. Intraduodenal or IV administration of avanafil potentiated penile tumescence in rabbits, dogs and monkeys.
- Secondary pharmacodynamics studies demonstrated that avanafil did not affect nitric oxide synthase activity, inhibit the adenosine receptor, or bind to the 17 other receptors and ion channels tested.
- Safety pharmacology studies found no or minimal effects of avanafil on respiratory, ocular, CNS, renal and gastrointestinal systems, or on coagulation and fibrinolysis. Avanafil did not alter ERG parameters in dogs, whereas comparable doses of sildenafil did. Adverse CNS effects (hypoactivity, tremors, ataxia) were observed only with high doses, and generally only after repeated dosing (relative animal:human exposures >127 times as unbound AUC in rats and dogs). Avanafil potentiated the inhibitory effect of nitroprusside on human platelet aggregation but the effect was weaker than that of sildenafil.
- In vitro, avanafil inhibited a potassium channel (hERG) channels, and to a lesser extent sodium channels and L-type calcium channels. However, these effects are unlikely to occur clinically (IC_{50} for hERG inhibition >350 times the unbound C_{max}). Furthermore, avanafil decreased action potential duration in isolated Purkinje fibres, and did not

[12] Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

[13] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

adversely affect ECG parameters in dogs. Avanafil decreased blood pressure and increased heart rate to a similar or lesser extent than sildenafil.

- Avanafil enhanced the hypotensive effects of nitroglycerin in dogs at exposures lower than that expected clinically.
- Oral bioavailability was very low in rats and moderate in dogs, with extensive first pass metabolism in both species. Avanafil was rapidly absorbed and widely distributed, with melanin binding and associated retention in the uveal track. Plasma protein binding was very high in humans (99%) and lower in laboratory animals (91-96%).
- In males, avanafil was extensively metabolised in rats, with moderate metabolism in dogs and humans. Two major metabolites were identified in humans that were formed by hydroxylation (M4) and oxidative cleavage to open the pyrrolidine ring (M16), both of which were present in rats and dogs. Avanafil was predominantly excreted as metabolites via the biliary/faecal route.
- The CYP3A4 isoform was the main enzyme involved in avanafil metabolism, with CYP2C also involved to a lesser extent. Based on clinical unbound C_{max}, avanafil is unlikely to inhibit or induce CYP1A2, 2B6 or 3A4.
- Avanafil is a weak substrate for P-glycoprotein. Avanafil did not inhibit P-glycoprotein, but the concentrations tested were below anticipated intestinal concentrations. Inhibition of BCRP is likely in the intestine. However, the rapid absorption of avanafil is likely to minimise potential drug-drug interactions in the intestinal tract.
- Avanafil was well tolerated by rodents in acute toxicity studies at doses up to 2000 mg/kg PO.
- Repeat dose toxicity studies were conducted in CD-1 mice (13 weeks), SD rats (up to 26 weeks) and beagle dogs (up to 9 months, males only in pivotal study). Maximum exposures were high based on unbound AUC in rats and male dogs (127 to 589 times), and moderate based on total AUC in mice (16 to 35 times). The toxicity profile was consistent with known class effects of PDE5 inhibitors with effects on liver (hepatocellular hypertrophy), thyroid (hypertrophy), kidney and adrenal gland (both increased weight). Vascular inflammation and arteritis was also observed in dogs. In rats, mild anaemia occurred at high doses with changes in erythrocyte parameters also observed in dogs. Overall, the effects of avanafil were generally mild and occurred only at high exposure margins.
- Avanafil was not mutagenic in bacterial reverse mutagenesis assays, or clastogenic in vitro (mammalian chromosome aberration assays in Chinese hamster ovary and lung cells). Avanafil was positive in the mouse lymphoma assay in the presence of metabolic activation. However, the in vivo studies were negative (mouse micronucleus assay and unscheduled DNA synthesis). The weight of evidence indicates that avanafil is not genotoxic.
- Two year carcinogenicity studies were conducted in mice and rats, with high exposure ratios achieved (up to 35 in mice based on total AUC, up to 589 in rats based on unbound AUC of that expected in humans). These studies indicated that avanafil is not carcinogenic.
- There was no adverse effect on sperm in dogs that received avanafil for 9 months (relative animal: human exposure 127 times), or in a rat fertility study at exposures 17 times that expected clinically (unbound AUC). Avanafil decreased sperm motility and increased the number of abnormal sperm in rats at high exposures (142 times that expected in humans) but these effects were reversible and did not impair fertility. In

females, high dose avanafil increased estrus cycle length and pre-implantation losses and decreased number of pregnant rats in association with maternal toxicity.

- Maternal toxicity was associated with decreased pup weight in rats and increased number of late resorptions in rabbits (relative animal:human exposures >138 and 44 by unbound AUC, respectively). In rabbits, there was a treatment-related increase in visceral variations (extra subclavian artery) at estimated exposures ≥7 based on mg/m^2. Body weight remained reduced post-weaning in offspring of rats that were exposed to 435 times clinical exposures, but there were no other adverse developmental effects.
- No ocular or skin phototoxicity was observed in rats with high avanafil exposures (142 times unbound AUC).
- The proposed limit for the process-related Impurity I-C in the API has been adequately qualified.

Nonclinical conclusions

- The nonclinical data were of high quality.
- The primary pharmacology studies support the proposed indication for avanafil.
- Secondary and safety pharmacology studies indicate a similar safety profile to other PDE5 inhibitors.
- Repeat-dose toxicity studies identified mild anaemia in addition to expected class effects. These effects are unlikely to be expressed clinically as they occurred only at high exposures and with daily dosing, which is not proposed for avanafil.
- The nonclinical data indicate a low genotoxic and carcinogenic potential for avanafil.
- Decreased sperm motility and abnormal sperm morphology were seen at very high exposures in rats, but were reversible and the finding was not replicated in dogs. Therefore, these findings are not considered clinically relevant.
- The proposed Pregnancy Category was B1, which should be changed to B3 based on the visceral variations observed in rabbits.
- Based on the nonclinical data evaluated in this report, registration of avanafil is supported.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Erectile dysfunction is a common condition in males aged 40 to 70 years, affecting 30% to 50% of that population. The condition may decrease quality of life for affected males and their partners. The current standard of care is oral treatment with phosphodiesterase 5

(PDE5) inhibitors, a number of which are currently approved for marketing in Australia, including sildenafil, tadalafil and vardenafil.

The sponsor states that 'Avanafil is a new PDE5 inhibitor for oral administration and was developed for its high selectivity for the PDE5 isoenzyme relative to other PDE5 inhibitors. Avanafil is rapidly absorbed following administration, reaching peak plasma concentration between 30 to 45 minutes in the fasted state giving the opportunity for clinical effectiveness as early as 15 minutes after administration.'

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 18 clinical pharmacology studies, including 12 that provided pharmacokinetic data and 9 that provided pharmacodynamic data.
- One population pharmacokinetic analyses.
- Four pivotal efficacy/safety studies.
- Three dose finding studies.
- One other efficacy/safety study.
- One Periodic Safety Update Report (PSUR).

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies all have statements of adherence to, and appear to have adhered to, Good Clinical Practice.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Study HP-01
		Study TA-140
	- Multi-dose	Study TA-02
	Mass balance	Study TA-07 Study TA-010

PK topic	Subtopic	Study ID
	Bioequivalence† - Single dose	Study TA-020
		Study TA-022
	Food effect	Study TA-020
	Hepatic impairment	Study TA-012
	Renal impairment	Study TA-013
	Elderly	Study TA-014
PK interactions	Ketoconazole, erythromycin, ritonavir	Study TA-0911
	Warfarin	Study TA-016
	Omeprazole, rosiglitazone, desipramine	Study TA-018
Population PK analyses	Healthy subjects	Study VIVU-RAS-002

† Bioequivalence of different formulations.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of avanafil has been adequately characterised. The dosing recommendations in the proposed PI with regard to hepatic impairment, renal impairment, age and drug interactions are supported by the PK data.

However, the PK data indicate that the 50 mg formulation was absorbed more rapidly than the 200 mg formulation; and that food increases T_{max} from 0.75 h to 2.0 h. These findings are important because the potential for rapid onset of action would be an advantage for avanafil in comparison with currently available treatments for ED.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 4: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on sperm function	Study TA-014,
		Study TA-021
	Effect on colour vision	Study TA-016
	Effect on QT interval	Study TA-140
PD Interactions	Warfarin	Study TA-016
	Glyceryl trinitrate	Study TA-04
	Ethanol	Study TA-015
	Doxazosin, tamsulosin	Study TA-017
	Enalapril, amlodipine	Study TA-019

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The pharmacodynamic data addressed the issues of disturbance of colour vision, effects on sperm function and QT prolongation. There was no effect on colour vision or sperm function. The data on QTc prolongation were equivocal.

Avanafil did not interact with ethanol or amlodipine. However, in combination with glyceryl trinitrate, enalapril or alpha blockers there were decreases in blood pressure that may be clinically significant.

Dosage selection for the pivotal studies

Study TA-01

Study TA-01 was a single blind, randomised, crossover, dose finding study of avanafil in conjunction with visual sexual stimulation (VSS) in subjects with erectile dysfunction. The study was conducted at 8 centres in the US from March 2002 to August 2002. The study included male subjects, 35 to 70 years of age, with a ≥ 6 month history of mild to moderate erectile dysfunction (ED); who were not using androgen therapy that had not been stable for 3 months or other prohibited therapies; with no history of chronic blood pressure <90/50 mmHg or >170/100 mmHg or recent stroke or myocardial infarction; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation. The study treatments were:

1. Avanafil either at 50 mg, 100 mg or 200 mg. These dose groups were recruited sequentially
2. Placebo
3. Sildenafil 50 mg

The study treatments were administered as three single doses on separate days in a random sequence. The primary outcome measure was measured using the RigiScan[14]. The reporters were blinded to treatment allocation. The outcome measures were:

- Time to ≥ 60% rigidity (tip and base):
- Duration of ≥ 60% rigidity (tip and base)
- Maximum rigidity (tip and base)
- Tumescent Activity Units TAU (tip and base)
- Rigidity Activity Units RAU (tip and base)
- Responses to the 5-point Erection Assessment Scale (EAS)

The safety outcome measures were vital signs and adverse events.

There were 297 subjects screened, and 83 were randomised and received study drug: 27 were treated with avanafil 50 mg, 28 with 100 mg, and 28 with 200 mg. One subject did not complete. All subjects were male, and the age range was 26 to 70 years. ED was organic for 50 (60.2%) subjects, psychological for 7 (8.4%) and mixed for 26 (31.3%). Race was Caucasian for 56 (67.5%) subjects and Black for 20 (24.1%).

For the efficacy outcome measures:

- Time to ≥ 60% rigidity (tip and base) decreased with increasing dose up to the 200 mg dose level with similar results to sildenafil, and improved compared to placebo.
- Duration of ≥ 60% rigidity (tip and base) increased with increasing dose up to the 200 mg dose level, with similar effect to sildenafil at the 100 mg and 200 mg dose levels.
- Maximum rigidity (tip and base) increased to the 200 mg dose level, was greater than placebo at all dose levels and was greater than sildenafil at the 200 mg dose level.
- Tumescent Activity Units TAU (tip and base) increased with increasing dose up to the 200 mg dose level, with greater effect than placebo at all dose levels and with similar effect to sildenafil at the 100 mg and 200 mg dose levels.
- Rigidity Activity Units RAU (tip and base) increased with increasing dose up to the 200 mg dose level, with greater effect than placebo at all dose levels and with similar effect to sildenafil at the 100 mg and 200 mg dose levels.
- Responses to the 5 point Erection Assessment Scale (EAS) was greater than placebo and sildenafil at the 40 minute time point for all dose levels, with increasing effect with dose up to the 200 mg dose level. There was similar effect for avanafil 200 mg and sildenafil 50 mg at the 80 minute and 120 minute time points.

Study TA-03

Study TA-03 was a double blind, randomised, three way crossover study to evaluate efficacy, onset of effect and duration of effect of avanafil 200 mg at home in subject with mild to moderate ED. The study was conducted at 3 centres in the US from July 2003 to January 2004. The study included males, 35 to 70 years of age, with a ≥ 3 month history of unsatisfactory sexual intercourse due to mild to moderate ED; in a monogamous, heterosexual relationship for ≥ 3 months; not using androgen therapy that had not been stable for 3 months; with no history of chronic high or low blood pressure defined as <90/50 or >170/100 mmHg or recent stroke, myocardial infarction, or life-threatening

[14] The RigiScan® Monitor is an ambulatory data logging unit that measures and records penile rigidity and tumescence.

arrhythmia; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation.

The study treatments were 6 individual doses of each of avanafil 200 mg 5 to 10 minutes prior to intercourse, avanafil 200 mg 2 h prior to intercourse and sildenafil 5 to 10 minutes prior to intercourse. There were no significant differences between the treatments in penetration success rate. Intercourse success rate was lower with avanafil at 5 to 10 minutes compared to the other two treatments. There was no significant difference between the treatments in time from dosing to achieving erection sufficient for intercourse. There was no significant difference between the groups in the Global Assessment Questionnaire or the Erectile Function Domain score.

Study TA-05

Study TA-05 was a double blind, randomised, parallel group, dose finding study to evaluate the safety and efficacy of avanafil for the treatment of mild to moderate ED. The study was conducted at 22 centres in the US from April 2004 to May 2005. The study included males 35 to 70 years of age, with a ≥6 month history of mild to moderate ED that did not result from spinal cord injury, diabetes, or radical prostatectomy; in a monogamous, heterosexual relationship for the 3 months; with no history of chronic blood pressure <90/50 or >170/100 mmHg or recent stroke, myocardial infarction, or life threatening arrhythmia; and with no significant medical condition or social problem that would interfere with study evaluations or otherwise contraindicate study participation.

The study treatments were: avanafil 50 mg, avanafil 100 mg, avanafil 200 mg, avanafil 300 mg and placebo. At least 6 doses of study drug to be taken 30 minutes prior to initiating sexual activity over a 12 week period. Subjects were randomised to treatment group. The outcome measures were: successful penetration, successful intercourse, and the Erectile Function Domain score (EFS) from the IIEF Questionnaire.

A total of 460 subjects were screened, 371 entered run-in period, and 295 were randomised: 57 to 50 mg, 61 to 100 mg, 59 to 200 mg, 59 to 300 mg and 59 to placebo. Of the randomised subjects 284 (96.3%) were included in Intent-to-Treat (ITT) population. The age range was 32 to 70 years, 243 (85.6%) were Caucasian and 29 (10.2%) were Black; for 36 (65.5%) the ED was of organic aetiology, four (7.3%) psychological, and 15 (27.3%) mixed. There were a higher proportion of subjects with mixed aetiology in the 100 mg and 200 mg groups. Erectile Function Domain scores were similar at baseline and end of run-in.

Penetration success rate increased with increasing dose, and was statistically significant compared with placebo at the 100 mg and 300 mg dose levels. Intercourse success rate also increased with dose up to the 300 mg dose level, and was significantly greater than placebo at all dose levels. There was an improvement in Overall Erectile Function Domain score relative to placebo at all dose levels, but there was a plateau in effect from the 100 mg dose level. There were similar improvements in: percent of erections that achieved some enlargement, percent of times satisfied with erection and percent of times satisfied with sexual experience. There were improvements in the Erectile Function Scores from the IIEF Questionnaire, for all the dose levels, that appeared to plateau at the 100 mg dose level. The Global Assessment Question responses improved with increasing dose, and were significantly improved compared to placebo at all dose levels.

Evaluator's overall conclusions on the dose finding studies

The dose finding studies were most supportive of the 100 mg dose level. The 300 mg dose level did not offer any advantage over the 200 mg dose level. The sponsor was justified in taking the 50 mg, 100 mg and 200 mg dose levels through to further development.

Efficacy

Studies providing efficacy data

Four pivotal efficacy/safety studies and one other efficacy/safety study were submitted. For details see Attachment 2 Extract from the Clinical evaluation report (CER).

Evaluator's conclusions on efficacy

Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED. The 100 mg and 200 mg dose levels were both superior to 50 mg. In Study TA-301, in subjects with mild to severe ED, the mean (SD) change from baseline in % successful penetration was 7.1 (32.07) % for placebo, 18.9 (35.51) % for avanafil 50 mg, 27.3 (35.17) % for 100 mg and 29.0 (35.90) % for 200 mg. The mean (SD) change from baseline in % successful intercourse was 14.4 (27.63) % for placebo, 27.8 (33.86) % for avanafil 50 mg, 43.2 (33.86) % for 100 mg and 44.6 (35.67) % for 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 2.9 (6.38) for placebo, 5.4 (7.54) for avanafil 50 mg, 8.3 (7.67) for 100 mg and 9.5 (7.03) % for 200 mg.

Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED. In Study TA-302, the mean (SD) change from baseline in % successful intercourse was 10.5 (27.73) % for placebo, 26.2 (33.71) % for 100 mg and 32.1 (32.94) % for 200 mg. The mean (SD) change from baseline in % successful penetration was 5.9 (31.16) % for placebo, 21.5 (37.19) % for 100 mg and 22.0 (35.00) % for 200 mg. The mean (SD) change from baseline in International Index of Erectile Function (IIEF) Erectile Function Domain Score was 1.8 (6.24) for placebo, 4.6 (7.00) for avanafil 100 mg and 5.3 (7.50) % for 200 mg.

Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy. In Study TA-303, the mean (SD) change from baseline in % successful intercourse was 4.8 (19.89) % for placebo, 18.3 (30.18) % for 100 mg and 21.1 (31.83) % for 200 mg. The mean (SD) change from baseline in % successful penetration was -0.4 (21.59) % for placebo, 15.3 (32.21) % for 100 mg and 20.8 (31.78) % for 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was 0.1 (3.56) for placebo, 3.6 (7.04) for avanafil 100 mg and 5.2 (7.00) % for 200 mg.

Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake. In Study TA-501 both active treatments has superior erectogenic effect ≤ 17 minutes after dosing compared to placebo, and there was no significant difference between the avanafil 100 mg and 200 mg dose levels. The LS mean (SE) erectogenic effect was 24.71 (2.911) % for avanafil 100 mg, 28.18 (2.876) % for 200 mg and 13.78 (2.905) % for placebo. In Study TA-301 the increase in the proportion of successful intercourse was from ≥15 minutes after ingestion. However, in Study TA-302, time of onset of effect was shorter for avanafil 100 mg than avanafil 200 mg for successful intercourse, successful penetration and Satisfaction with Sexual Experience.

The effects of avanafil appear to be maintained over a 52 week period. In Study TA-314, in subjects followed up for up to 52 months, at last study visit the proportion of subjects with successful intercourse was 67.7% for avanafil 100 mg and 66.3% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful intercourse was 76.62%, seven in the 100 mg with 97.32% success and ten in the 200 mg with 96.25% success. The proportion of subjects with successful penetration was 83.3% for avanafil 100 mg and 79.4% for 100 mg and 200 mg combined. At Week 52, there were seven subjects in the avanafil 50 mg group, and the proportion of attempts with successful penetration was 51.98%, seven in the 100 mg with

35.48% success and ten in the 200 mg with 71.89% success. Mean (SD) IIEF Erectile Function Domain score was 22.2 (8.57) for avanafil 100 mg and 22.7 (8.12) for 100 mg and 200 mg combined.

For Study TA-314, the efficacy analyses were performed using the data from the subjects last study visit, but are presented as a 52 week analysis. Hence these should be interpreted as the results for the last study visit. There were insufficient data in the other doses group to provide meaningful conclusions. The data also represent a responder analysis. A more useful analysis would be to present the results by study visit.

The outcome measures used in the clinical trials were clinically relevant. The statistical measures, including those addressing imputation and multiplicity, were appropriate. The population of patients studied in the clinical trials was similar to that intended for marketing in Australia. The PI reflects this study population.

The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet.

Safety

Studies providing safety data

There were no pivotal studies that assessed safety as a primary outcome. The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by AEs, clinical laboratory tests, vital signs and ECGs.

Dose response and no-pivotal efficacy studies

The dose response and non-pivotal efficacy studies provided safety data, as follows: AEs, clinical laboratory tests and ECGs.

Clinical pharmacology studies

The clinical pharmacology studies provided safety data, as follows: AEs, clinical laboratory tests and ECGs.

Patient exposure

There were 2144 subjects exposed to avanafil in the development program, including 644 in Phase 1, 360 in Phase II and 1140 in Phase III.

- In Study TA-01, there were 27 subjects exposed to a single dose of avanafil 50 mg, 28 to 100 mg, and 28 to 200 mg
- In Study TA-03, there were 49 subjects exposed to up to 12 doses of avanafil 200 mg.
- In Study TA-05 subjects received up to 18 doses and a median of 16 doses. There were 57 subjects exposed to avanafil 50 mg, 61 to 100 mg, 59 to 200 mg, and 59 to 300 mg.
- In Study TA-301 there were 150 subjects exposed to avanafil 50 mg, 161 to avanafil 100 mg and 162 to avanafil 200 mg for up to 12 weeks. In the study there were 144 (22.3%) subjects aged ≥65 years, 233 (36.2%) subjects with a history of hypertension and 61 (9.5%) subjects with a history of coronary artery disease.

- In Study TA-302, conducted in subjects with diabetes mellitus, there were 127 subjects exposed to avanafil 100 mg and 131 to 200 mg for up to 12 weeks. In the study there were 105 (26.9%) subjects aged ≥65 years, 260 (67.0%) subjects with a history of hypertension, and 54 (13.9%) with a history of coronary artery disease.
- In Study TA-303, conducted in subjects with a history of bilateral nerve-sparing retropubic radical prostatectomy, there were 99 subjects exposed to avanafil 100 mg and 99 to 200 mg for up to 12 weeks. There were 48 (16.1%) subjects aged ≥65 years, 125 (41.9%) subjects with a history of hypertension, 38 (12.8%) with other cardiovascular disease and seven (2.3%) with coronary artery disease.
- In Study TA-501, there were 146 subjects exposed to avanafil 100 mg and 146 to 200 mg, with a median number of doses of 11. There were 129 (29.3%) subjects were aged ≥65 years.
- In Study TA-314, there were 153 subjects exposed to avanafil for ≥12 months and 493 for ≥6 months.

Safety issues with the potential for major regulatory impact

Liver toxicity

The data did not identify any safety issues with regard to liver toxicity. However, the sponsor did not provide a listing of subjects who fulfilled the criteria of Hy's law.

Haematological toxicity

The data did not identify any safety issues with regard to haematological toxicity.

Serious skin reactions

The data did not identify any safety issues with regard to serious skin reactions.

Cardiovascular safety

The data identified a potential safety issue with regard to prolongation of QTc[15]. For the 800 mg dose level, at 3 h post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms, the upper 90% CI being >10, which is the level of regulatory concern. The data were incomplete because the results for QTcB and QTcF were not provided in the submission.

Unwanted immunological events

The data did not identify any safety issues with regard to serious skin reactions.

Evaluator's conclusions on safety

The rates of treatment emergent AEs (TEAEs) were higher in the avanafil treatment groups compared to placebo. Headache was more common in the avanafil groups and appeared to be dose related. Up to 13% of subjects in the avanafil 200 mg groups reported headache. The risk of TEAE was not influenced by age, race, diabetes status or coronary artery disease.

[15] The QT interval is dependent on the heart rate in an obvious way (the faster the heart rate the shorter the QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia. Modern computer-based ECG machines can easily calculate a corrected QT (QTc), but this correction may not aid in the detection of patients at increased risk of arrhythmia, as there are a number of different correction formulas. One clinical correction is to use Bazett's formula calculating the heart rate-corrected QT interval (QTcB). Fridericia has published an alternative correction formula using the cube-root of RR.

Treatment related TEAEs were more common with avanafil than placebo and the rate increased with dose. Up to 23% of subjects in the avanafil 200 mg group had TEAEs attributed to treatment. TEAEs attributed to treatment included headache, flushing and nasal congestion. All of these AEs appeared to be dose related. At doses of avanafil 800 mg all subjects reported TEAEs.

There was one death but it was not attributed to treatment. Serious AEs (SAEs) were uncommon and did not have any apparent pattern

Drug adverse event (DAE) was uncommon and did not have any apparent pattern.

Elevations in alanine transaminase (ALT) were uncommon in the avanafil treatment groups and none were considered to be clinically significant by the sponsor. However, the sponsor has not stated whether any subjects fulfilled the criteria of Hy's law for drug induced liver injury. There were no clinically significant abnormalities in renal function or haematology reported during the development program for avanafil. Shifts from normal to abnormal occurred at similar rates for avanafil and placebo.

In the Thorough QT study[16], although there were no concerns with regard the 100 mg dose level, for the 800 mg dose level, at 3 h post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) ms. The upper 90% CI was >10, which is the level of regulatory concern. It is the opinion of the Sponsor that this result is spurious because the 800 mg dose resulted in an increase in heart rate compared to the other three treatments. However, the results for QTcB and QTcF were not provided in the report.

Abnormalities in vital signs were uncommon with avanafil and did not appear to be clinically significant.

In combination with glyceryl trinitrate (GTN) there was an increased risk of headache, dizziness and nausea with avanafil, which was similar to the risk with sildenafil.

There were an adequate number of subjects exposed to avanafil for long term use: >100 subjects have been exposed for >12 months and >300 subjects have been exposed for > 6 months. In Study TA-314 there were 153 subjects exposed to avanafil for ≥ 12 months and 493 for ≥ 6 months.

There were adequate subjects aged ≥ 65 years in the development program: 426 in the pivotal studies. There were also adequate subjects with comorbidities such as hypertension or coronary artery disease.

There were no data submitted regarding potential interactions with treatments for premature ejaculation, such as dapoxetine, or with illicit drugs.

First round benefit-risk assessment

First round assessment of benefits

The benefits of avanafil in the proposed usage are:

- Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED.

[16]ICH Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy.
- Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake.
- The effects of avanafil appear to be maintained over a 52 week period.

The benefits of avanafil were clinically significant.

Food does not appear to have a clinically significant effect on rapidity of onset of effect. Although, compared to the fasted state, food delayed absorption and decreased C_{max} for avanafil overall exposure was unchanged. In the pivotal studies, avanafil had rapid onset of effect regardless of food intake. Hence, in the opinion of this evaluator, there is no need for dosing instructions with regard to food.

The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet. There were differences in the rate of absorption between the 50 mg and 200 mg tablet sizes that may affect the speed of onset of effect.

First round assessment of risks

The risks of avanafil in the proposed usage are:

- Avanafil has a dose related risk for headaches, flushing and nasal congestion. Headache was more common in the avanafil groups and appeared to be dose related. Up to 13% of subjects in the avanafil 200 mg groups reported headache.
- Overall, the rates of TEAEs were higher in the avanafil treatment groups compared to placebo. The risk of TEAE was not influenced by age, race, diabetes status or coronary artery disease.
- Treatment related TEAEs were more common, and the rate increased with dose. Up to 23% of subjects in the avanafil 200 mg group had TEAEs attributed to treatment. TEAEs attributed to treatment included headache, flushing and nasal congestion. All of these AEs appeared to be dose related. At doses of avanafil 800 mg all subjects reported TEAEs.
- There were no deaths in the development program that were attributed to avanafil. There was one death reported in the development program for avanafil: self-inflicted gunshot injury.
- In combination with GTN there were increased risks of headache, dizziness and nausea with avanafil, which were similar to the risks with sildenafil.
- SAEs were uncommon and did not have any apparent pattern
- DAE was uncommon and did not have any apparent pattern.

There are a number of potential risks that require clarification:

- Elevation in liver enzymes was reported in the avanafil treatment groups and the sponsor has not stated whether any subjects fulfilled the criteria of Hy's law.
- In the Thorough QT study, although there were no concerns with regard the 100 mg dose level, for the 800 mg dose level, at 3 h post dose the placebo corrected mean (90% CI) change in QTcI (Individual correction) was 7.9 (5.5 to 10.2) msec. The upper 90% CI was >10, which is the level of regulatory concern. It is the opinion of the sponsor that this result is spurious because the 800 mg dose resulted in an increase in heart rate compared to the other three treatments. However, the results for QTcB and QTcF were not provided in the report.

First round assessment of benefit-risk balance

The benefit-risk balance of avanafil, given the proposed usage, is unfavourable. This is because there are safety issues that require clarification. If the sponsor can satisfactorily clarify that there were no cases of drug induced liver injury and no QTc prolongation of regulatory concern in the development program then the benefit-risk balance of avanafil would become favourable.

First round recommendation regarding authorisation

The application to register Spedra (avanafil) should be rejected.

The reason for rejection is that there are unresolved safety issues regarding whether any cases of drug induced liver injury and/or QTc prolongation of regulatory concern exist in the data from the development program of avanafil.

Clinical questions

Pharmacokinetics

1. In the PK data, the 50 mg tablet formulation was absorbed more rapidly than the 200 mg. Did the subsequent clinical trial data indicate any differences in the rate of onset of effect?
2. In the PK data, food increased T_{max} from 0.75 h to 2.0 h. Did the subsequent clinical trial data indicate any effect of food on the rate of onset of effect?

Pharmacodynamics

3. From Study TA-140, please provide the tabulations of the placebo corrected change from baseline for QTcF and QTcB, with 90% CI, for the time points 0.5, 1, 1.5, 2, 3, 4, 6, 12, 18 and 23 h after dosing for avanafil 100 mg, avanafil 800 mg and moxifloxacin 400 mg.

Efficacy

4. The formulations studied in the pivotal studies were either the 50 mg tablet or the 100 mg tablet. None of the subjects in the pivotal studies received the 200 mg tablet. There were differences in the rate of absorption between the 50 mg and 200 mg tablet sizes that may affect the speed of onset of effect. Does the Sponsor have data that demonstrate the 200 mg tablet size has similar time to onset of effect as either the 50 mg or 100 mg tablet sizes?
5. For Study TA-314, please provide summary tabulations of efficacy measures by study visit.

Safety

6. Please provide summary tabulations for QTcF and QTcB from Study TA-140.
7. In Study TA-314 one subject developed a clinically significant ECG abnormality on active treatment. Please provide a description of the ECG abnormalities.
8. Does the sponsor have data regarding potential interactions between avanafil and treatments for premature ejaculation, such as dapoxetine, or with illicit drugs?

9. Please provide a tabulation, and case descriptions, for all subjects with ALT or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) and bilirubin >2 x ULN.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefit

After consideration of the responses to the clinical questions, the benefits of avanafil in the treatment of erectile dysfunction in adult men are unchanged.

- Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED.
- Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve-sparing radical prostatectomy.
- Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake.
- The effects of avanafil appear to be maintained over a 52 week period.
- No benefit clinical benefit of 200 mg over 100 mg has been demonstrated.

Second round assessment of risks

After consideration of the responses to the clinical questions, the following concerns remain:

1. The 200 mg dose formulation was not used in the key pivotal studies; therefore the clinical efficacy of this formulation is unknown. Bioequivalence has been satisfactorily demonstrated based on the EU guidelines for C_{max} and AUC, but there is variability in T_{max} between different formulations. It is possible that this variability in T_{max} may have an impact on the onset and duration of action. A delayed onset of action may have a clinically significant impact on its effect on erectile function.
2. A QT study at a dose of 200 mg has not been performed and the results of the QT study for the 800 mg dose are equivocal. Thus, the safety of the 200 mg dose in relation to QT prolongation is unknown.
3. The most common adverse effects of avanafil, such as headache, flushing and nausea, are dose proportional and more common at a higher dose.

Second round assessment of benefit-risk balance

There are clinical and statistically significant benefits of avanafil at a dose of 100 mg for the treatment of erectile dysfunction in males. The risks of avanafil at this dose are acceptable.

The clinical data submitted does not demonstrate superiority of a 200 mg dose over a 100 mg dose. There are more adverse effects observed with larger doses. The impact of the 200 mg dose on the QT interval is unknown. Although a repeat QT/QTc study using a dose of 200 mg of avanafil would help resolve the later issue, the benefit-risk balance of the large body of clinical evidence collected about the safety and efficacy of avanafil at a dose of 200 mg will remain unchanged.

Although disabling, erectile dysfunction is not associated with significant morbidity or limited life expectancy. The risks to the health and wellbeing of the population as a consequence of not approving the 200 mg dose are smaller than the risks associated approving this larger dose and formulation.

Second round recommendation regarding authorisation

The clinical evaluator recommends approval of avanafil for the '*Treatment of erectile dysfunction in adult men'* subject to the following:

1. A limitation of the dose to 100 mg daily
2. That the PI be amended to include
    a. A warning about the potential for QT prolongation with overdose
3. The addition of risks to the RMP including:
    a. Potential risk: prolongation of the QT interval with high exposure
    b. Missing Information: the use of avanafil with illicit drugs

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP version 4.1 dated 30 June 2013 (data lock point 10 October 2012) with the Australian Specific Annex version 1.1 dated 1 June 2015) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Summary of ongoing safety concerns

Important identified risks	Pre-existing cardiovascular disease
	Prolonged erection (priapism)
Important potential risks	Hypotension/increased hypotensive effect
	Non-artertitic anterior ischaemic optic neuropathy
	Sudden hearing loss
Important missing information	Very elderly males > 70 years of age
	Adult males with ED due to spinal cord injury

	Adult males with significant pre-existing cardiovascular disease
	Adult males with severe renal or hepatic impairment
	Patients with retinitis pigmentosa
	Effect of avanafil in patients with bleeding disorders or active peptic ulceration
	Effect of avanafil on spermatogenesis in healthy adult males and adult males with mild ED
	Effects of avanafil on multiple parameters of vision

Pharmacovigilance plan

Routine pharmacovigilance has been proposed to monitor all safety concerns. The sponsor is also committed to provide evaluation of the use and reported adverse events in elderly males (>70 years of age) compared to males less than 70 years of age in the PSURs. Two studies have been conducted to collect evidence on the 'effect of avanafil on spermatogenesis in healthy adult males and adult males with mild ED' and 'effect of avanafil on multiple parameters of vision' respectively.

Risk minimisation activities

Routine risk minimisation activities through information provided in the Australian PI and Consumer Medicine Information (CMI) are proposed to mitigate all the safety concerns. The sponsor has also provided the detailed text to be included in these documents.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and an evaluation of the sponsor's responses.

Table 6: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the non-clinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	*The sponsor acknowledges the above comments and would like to confirm that no safety concerns have been identified from the clinical and pre-clinical evaluation reports which need to be addressed in the RMP.*	The sponsor's response is satisfactory.
2. The sponsor should provide the date and version number of the ASA in the document.	*The ASA has been updated to include date and version control. Please find enclosed the updated document.*	The sponsor's response is satisfactory.
3. The list of safety concerns covers most of the severe adverse effects that have been identified for other PDE5 inhibitors. The following are pharmacological class effects and safety issues identified for other PDE5 inhibitors that are missing from the above list: a. Bleeding disorders b. Migraine c. Seizures d. Effect on QT interval e. Interaction with CYP3A4 inhibitors.	*The sponsor acknowledges the aforementioned comment and would like to provide a justification for each of the aforementioned safety issues.* *Bleeding disorders* *Effect of avanafil in patients with bleeding disorders or active peptic ulceration is mentioned in the Avanafil EU RMP as well as in Australian Specific Annex (ASA) as 'missing information'. 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 (EU Summary of product Characteristics (SmPC) Avanafil).*	The sponsor's commitment to monitor the events and report in the PSURs is acceptable. Detailed comments regarding '*effect on QT interval*' are under '*Additional recommendations*'.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	Concerning this safety issue no specific data have been collected during avanafil clinical trial development or post marketing experience. This issue seems not to be reported for all the other PDE 5 inhibitors drugs: for example it is not included in the vardenafil ASA (as can be deduced from AusPAR February 2011). *On the base of this information, as no specific data are available for avanafil and as the issue does not appear to be related to all the drug class of PDE5 inhibitor, the sponsor proposed to continue to manage it as 'missing information' and to monitor it through PSURs.* *Migraine* *No specific data have been collected during avanafil clinical trial development and in the postmarketing experience concerning migraine. This safety issue is also not mentioned for other PDE5 inhibitors, for example in the vardanafil ASA (as it can be deduced from AusPAR February 2011) or in the tadalafil ASA (as it can be deduced from AusPAR February 2013).* *Reports of Migraine will be monitored through PSURs but currently the sponsor does not identify any specific elements justifying the insertion of it as an important risk in the RMP.* *Seizures* *No specific data have been collected during avanafil clinical trial development or in the postmarketing experience concerning seizures. In the vardenafil ASA (as it can be deduced from AusPAR February 2011) seizure is mentioned as a potential risk but it is also reported in the PI as a rare (> 0.01% to < 0.1%) adverse drug reaction in patients as collected in clinical trials world-wide and in the post marketing period. Other*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	PDE5 inhibitors, such as tadalafil (its ASA can be deduced from AusPAR February 2013) do not mention it as an important risk. *Reports of Seizures will be monitored through PSURs but currently the sponsor does not identify any specific elements justifying insertion of it as an important risk in the RMP.* *Effect on QT interval* *A clinical study (TA-140) to evaluate the avanafil effects (therapeutic and supratherapeutic dosing) on QTc prolongation in healthy male subjects has been conducted. The four different algorithms (Bazzet, Fridericia, QTcI (individual) and the Beat-to-Beat algorithms) were used to calculate QTc in the clinical Study TA-140. The results from the study showed that the PDE-5 mechanism of action of avanafil, like vardenafil and sildenafil, produces vasodilatory induced reflex tachycardia resulting in autonomic changes to the QT-RR interval relationship resulting in QTc elevations. Although these changes may transiently exceed the QT interval upper 90% CI threshold of 10 ms for a positive E14 TQT study, there was no relationship between these effects and drug exposure. The beat-to-beat analyses demonstrated that the % of beats exceeding the normal QT interval 97.5% reference bounds (that is, the % outlier beats) is not increased and within normal physiological boundaries, mitigating the concern for potential impairment of cardiac repolarization.* *In all the postmarketing data, only 1 case of not better specified arrhythmia has been collected. No element, at the present, is identified to insert 'Effect on QT interval' as an important risk in the avanafil RMP and it will be*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	monitored through PSURs. *Interaction with CYP3A4 inhibitors* *No specific data have been collected during avanafil clinical trial development and in the post marketing experience concerning this issue. This safety issue is also not mentioned for other PDE5 inhibitors, for example in the tadalafil ASA (as it can be deduced from AusPAR February 2013). This safety issue is also not mentioned for other PDE5 inhibitors, for example in the vardanafil ASA (as it can be deduced from AusPAR February 2011) or in the tadalafil ASA (as it can be deduced from AusPAR February 2013).* *Reports of Migraine will be monitored through PSURs but currently the sponsor does not identify any specific elements justifying inserting it as an important risk in the RMP.*	
4. Neither study (1889-1 or 1889-2) involved Australian patients. However, all findings are considered relevant and applicable to the local context. The sponsor should provide an update on significant safety findings from Studies1889-1 (TA-401) and 1889-2 (TA-402).	*The sponsor acknowledges the comment and would like to provide an update on the aforementioned studies.* *Phase IV clinical trial Study 1889-1 (TA-401) was completed in January 2015. Its primary objective was to assess the effect of daily treatment with avanafil 100 mg on spermatogenesis over a period of 26 weeks. The secondary objective was to evaluate the safety and tolerability of daily use of avanafil in these subjects. A total of 181 subjects (healthy adult male subjects and male subjects with mild erectile dysfunction with normal sperm concentration) have been randomised in the study. This study has demonstrated that daily dosing with avanafil 100 mg for 26 weeks was generally well tolerated, and was not associated with any untoward effects on*	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	sperm concentration, count, motility, or morphology. Avanafil treatment was safe and well tolerated. The overall incidence of Treatment Emergent Adverse Events (TEAEs) was slightly higher in the placebo group (22.0%) than in the avanafil 100 mg group (15.6%). The incidence of study drug related TEAEs was higher in the avanafil 100 mg group (5.6%) than in the placebo group (2.2%). Most of the TEAEs were mild or moderate in severity. The most frequently reported TEAE for the placebo group and the avanafil 100 mg group was headache (3.3%). No subject died during this study. There was one SAE during this study, which occurred in the placebo group. The percentages of subjects who discontinued study drug due to an adverse event were low and similar for the two treatment groups. No clinically important differences among treatment groups were noted in the mean changes in safety laboratory parameters or physical examination findings at the end of treatment. For all treatment groups, mean systolic blood pressure (SBP)/diastolic blood pressure (DBP) values and mean heart rate values at the end of treatment were similar to those at randomisation. *Phase IV clinical trial study 1889-1 (TA-402) was initiated by VIVUS, Inc. on 26 December 2013 and completed on 22 January 2014. 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 volunteers. In this single centre, randomised, double blind, placebo controlled, parallel study, subjects were randomised to receive a single dose of 200 mg avanafil or placebo. Visual parameters were assessed at baseline and at*	

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	selected post-dose time points approximate to C_{max} (that is, H 1) and at H 24 as a post-dose recovery assessment. Safety was assessed throughout the study. The study indicates that there was a significantly greater decrease in pupil diameter one h after treatment with avanafil (versus placebo), this observation is consistent with the vasodilatory effects of avanafil, and was not considered to be clinically significant. Mean changes for all other assessed ophthalmic parameters were comparable between avanafil and placebo, with minimal changes from baseline observed. There were no ophthalmic events reported as AEs in this study. The study concluded that there were no safety concerns with regard to the ocular assessments of visual acuity, pupillometry, colour vision discrimination, and IOP evaluations performed in this study.	
5. In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the PI be updated to include the following statement under '*Use in the elderly*' as men >70 years remains missing information: '*Data on patients older than 70 years are limited*'. (As in the EU SmPC)	*The sponsor notes the comment. Any proposed changes will be made to the PI after the Delegates overview.*	The evaluator has noted the sponsor's response. The recommendation on the PI document remains, for consideration by the Delegate.

Summary of recommendations

It is considered that the sponsor's response to the TGA has adequately addressed most of the issues identified in the RMP evaluation report.

Additional recommendations are detailed below.

Outstanding issues

Issues in relation to the RMP

The recommendation on the draft Product Information remains, awaiting consideration by the Delegate.

Additional recommendations

The evaluator supports the clinical evaluator's comments.

The sponsor has provided a justification as to why QT interval prolongation is not considered a safety concern for avanafil (see sponsor's response to Recommendation 4 under section 4 'Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)'). The RMP evaluator agrees with the clinical evaluator that patients with risk factors for cardiac disease could be more sensitive to the effects of an increased dose of avanafil. The sponsor should add 'QT interval prolongation' as a potential risk to the ASA and undertake to give specific consideration to arrhythmia events in the PSURs.

In the EU-RMP, the sponsor acknowledges the possibility of recreational use and misuse of PDE5 inhibitors, including the use of PDE5 inhibitor with other illicit drugs including ketamine and amyl nitrate which may lead to serious hypotension. The evaluator has noted that concomitant use of avanafil and nitrates is listed under 'Contraindication'. This routine risk minimisation measure is considered adequate. The sponsor should undertake to report all the serious adverse events related to recreational use and off-label use in the PSURs.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP version 4.1 dated 30 June 2013 (data lock point 10 October 2012) with the Australian Specific Annex version 1.1 dated 1 June 2015 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has recommended approval for avanafil. Avanafil is an immediate release oral tablet designed to have a rapid onset of action and packaged in blister foils. Two formulations were used in clinical studies (bioequivalent) with the second formulation being the one used in the Phase III studies and proposed for registration. The product has a shelf life of 4 years when stored below 25°C. Food delays the absorption of avanafil and reduces its maximum concentration but with no effect on extent of exposure. Avanafil exhibits linear pharmacokinetics over the dosing range.

Nonclinical

The nonclinical evaluator has no objections to the registration of avanafil. The dossier was of high quality and the pharmacology studies support the proposed indication. The substance has a similar safety profile to other PDE5 inhibitors based on its secondary and safety pharmacology studies. Repeat dose toxicity studies showed mild anaemia in

addition to the expected class effects (liver, thyroid, kidney and adrenal glands) which was evident at high exposures with daily dosing. Avanafil has a low genotoxic and carcinogenic potential and the proposed Pregnancy Category should be B3 based on visceral variations in rabbits. Decreased sperm motility and abnormal sperm morphology were seen at very high exposures in rats, but were reversible and the finding was not replicated in dogs, thus not considered clinically relevant. Avanafil was also a weak inhibitor of PDE6. It did inhibit hERG channels in vitro however this effect was thought to be unlikely clinically and it did not alter ECG parameters in dogs. Avanafil decreased blood pressure and increased heart rate, similar to sildenafil. It's metabolised mainly by CYP3A4 with CYP2C to a lesser extent and is a weak substrate for P-glycoprotein.

Clinical

The clinical evaluator has recommended approval for avanafil subject to the following:

a. A limitation of the dose to 100 mg daily
b. That the PI be amended to include a warning about the potential for QT prolongation with overdose
c. The addition of risks to the RMP including:
    i. Potential risk- prolongation of the QT interval with high exposure
    ii. Missing Information: the use of avanafil with illicit drugs

Pharmacokinetics

The studies noted the following findings:

- T_{max} for avanafil was 0.75 h (fasted state) and 2 h (fed state).
- The 50 mg, 100 mg and 200 mg tablet strengths are bioequivalent in the fasted state.
- Absorption was faster with the 50 mg tablet strength compared to the 200 mg tablet strength: median T_{max} 0.5 h compared to 0.75 h respectively.
- Compared to the fasted state, food delays absorption and decreases C_{max} for avanafil, but overall exposure is unchanged.
- There was dose proportionality between 100 mg and 800 mg single doses for avanafil and metabolites M4 and M6.
- There was no accumulation with twice daily dosing of 200 mg over a one week period.
- The volume of distribution (Vd) was 47 to 83 L in one study and 89 to 102 L in another with high protein binding.
- Avanafil is predominantly metabolised in the liver by CYP3A4 and to a lesser extent CYP2C9.
- The predominant route of elimination of avanafil is in the faeces (62% of the dose) then urine (21% of the dose).
- The active M4 metabolite is predicted to account for approximately 4% of total pharmacological activity.
- Apparent clearance (CL/F) is around 60 L/h. Renal clearance of unchanged avanafil is in the range 0.037 to 0.051 mL/min.
- Terminal half-life of 6 to 17 h.

- Hepatic impairment: Mildly impaired patients showed no significant change in exposure and moderately impaired patients showed 60% decrease in C_{max} but AUC unchanged.
- Renal impairment: Mildly impaired patients showed no significant change in exposure. Moderately impaired patients showed no significant change in exposure.
- There was no significant difference in PK parameters between healthy young males and healthy elderly males for a 200 mg single dose.
- The population PK study indicated that CYP inhibitors result in a clinically significant increase in exposure to avanafil.
- Ketoconazole increased exposure to avanafil thirteen fold (contraindication), ritonavir increased exposure to avanafil thirteen fold (contraindication)
- Erythromycin increased exposure to avanafil three fold.
- Avanafil did not show clinically significant effects on exposure to warfarin, omeprazole, rosiglitazone, desipramine or amlodipine.
- Amlodipine increased exposure to avanafil by 60% and increased $t_{1/2}$ by 2 h.

Pharmacodynamics

The studies noted the following findings:

- Avanafil 200 mg did not affect semen volume, sperm concentration, total sperm count, % normal forms, total motile count, % motility, forward progression, WHO calculated forward progression or vitality.
- In combination with warfarin, there was no significant effect of avanafil on the measures of colour vision.
- A Thorough QT study did not demonstrate a significant effect on the QT interval at the 100 mg dose but an 800 mg dose (4 times the proposed maximum dose) at 3 h had an upper bound of the 90% CI of 10.2 ms which is >10ms (threshold of regulatory concern).
- There was a clinically significant fall in sitting systolic blood pressure (SBP), of approximately 4 mmHg, when glyceryl trinitrate (GTN) was administered 0.5 h after avanafil, but not when administered 1 h or more after avanafil.
- Combining avanafil with ethanol (single standard measure) produced a mean fall in SBP of 3.53 mmHg, a fall in DBP of 4.54 mmHg and a rise in pulse rate of 9.33 beats per minute (bpm).
- Combining avanafil with doxazosin or tamsulosin or enalapril resulted in decreases in blood pressure that may be clinically significant for some patients.
- The addition of avanafil to patients on amlodipine did not result in clinically significant changes in blood pressure or heart rate.

Efficacy

The doses selected for the pivotal studies was based on three studies (TA-01, TA-03 and TA-05) that examined doses of 50 mg, 100 mg, 200 mg and 300 mg in males 35 to 70 years of age with mild to moderate erectile dysfunction (ED). The studies supported an increasing efficacy with dose with some plateauing at the 100 mg dose level, but the 300 mg dose did not offer an advantage over the 200 mg dose. Thus the 50, 100 and 200 mg

doses were taken forward for investigation. One of the studies (TA-03) that compared two different timings of administration (5 to 10min and 2 h prior to intercourse) of a 200 mg dose showed no significant difference between the treatments in time from dosing to achieving erection sufficient for intercourse, no significant differences between the treatments in penetration success rate but intercourse success rate was lower with avanafil given at 5 to 10 minutes prior to intercourse.

The pivotal efficacy and safety data are derived from four studies (TA-301, TA-302, TA-303 and TA-501) of up to 12 weeks duration along with one long term open label extension study (TA-314) for 52 weeks. The first three studies were of similar design (randomised double blind placebo controlled) but assessed different populations (mild-severe ED, mild-moderate ED+diabetes, ED+bilateral nerve sparing radical prostatectomy) and all subjects were to take avanafil 30 minutes prior to intercourse. The fourth study (TA-501) in mild to severe ED examined the administration of avanafil 15 minutes prior to intercourse.

All patients were males ≥ 18 years of age with ED of at least 6 months duration (history of inability to achieve vaginal penetration on at least 50% of attempts at sexual intercourse without the use of medical therapy), in a monogamous heterosexual relationship, agreement to at least 4 attempts at intercourse per month, not to use any other treatments for ED, a 50% or greater failure rate in maintaining an erection long enough to allow successful intercourse as recorded in the subject diary during the run-in period and an IIEF erectile function domain score of 5 to 25, inclusive. The diabetes trial required a documented history of type 1 or 2 diabetes but excluded those with uncontrolled diabetes (glycosylated haemoglobin (HbA1c) > 9%), fasting blood glucose >15 mmol/L and history of three or more episodes of hypoglycemia requiring assistance within the last two years. The prostatectomy trial required patients 18 to 70 years of age, history of bilateral nerve-sparing retropubic radical prostatectomy for localized carcinoma of the prostate at least 6 months prior to screening, prostate carcinoma stage ≤ pT2 and Gleason score ≤7 (4 + 3), prostate-specific antigen (PSA) level at screening consistent with the absence of residual prostate cancer and history of sexual potency prior to radical prostatectomy that did not require routine medical therapy to achieve or maintain an erection. The fourth study had a slightly different inclusion criterion of history of mild to severe erectile dysfunction of at least 6 months duration, as evidenced by a greater than 50% failure rate in maintaining an erection of sufficient duration to allow successful intercourse, without the use of medical therapy. The general exclusion criteria were extensive but included many as expected for a PDE5 inhibitor, such as nitrate use, drugs inhibiting CYP3A4, hypotension, myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization, unstable angina, high risk arrhythmia, cardiomyopathy and non-arteritic anterior ischemic optic neuropathy.

The three primary efficacy measures for the first three studies (TA-301, TA-302, TA-303) were: change in the percentage of sexual attempts between the run-in period and the 12 week treatment period in which the subject was able to maintain an erection of sufficient duration to have successful intercourse (subject diary question 5, also referred to as Sexual Encounter Profile [SEP]3), change in the percentage of sexual attempts between the run-in period and the 12 week treatment period in which the subject was able to insert his penis into his partner's vagina (subject diary question 4, also referred to as SEP2) and change in IIEF erectile function domain score from baseline to end of the 12 week treatment period. The fourth study's (TA-501) primary endpoint was the per subject proportion of sexual attempts that had an erectogenic effect within approximately 15 minutes following dosing, where an erectogenic effect was defined as an erection sufficient for vaginal penetration and that enabled satisfactory completion of sexual intercourse. This was subsequently defined as being ≤ 17 minutes after dosing.

Study TA-301 (general ED) had 646 patients randomised (85% completion, age 23 to 88 years, 22% ≥65 years, 36% hypertension) with a mean time from ingestion to initiation of sexual activity of 58 minutes. The primary efficacy results were:

- Successful intercourse (SEP3): All the avanafil treatment groups were superior to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in % successful intercourse was:
  - 14.4 (27.63) % for placebo
  - 27.8 (33.86) % for 50 mg
  - 43.2 (33.86) % for 100 mg
  - 44.6 (35.67) % for 200 mg
- Successful penetration (SEP2): All the avanafil treatment groups were superior to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in % successful penetration was:
  - 7.1 (32.07) % for placebo
  - 18.9 (35.51) % for 50 mg
  - 27.3 (35.17) % for 100 mg
  - 29.0 (35.90) % for 200 mg
- IIEF EF domain score: The change was greater in all the avanafil treatment groups compared to placebo, and the 100 mg and 200 mg groups were superior to 50 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was:
  - 2.9 (6.38) for placebo
  - 5.4 (7.54) for 50 mg
  - 8.3 (7.67) for 100 mg
  - 9.5 (7.03) for 200 mg.

Secondary efficacy endpoints were supportive however subjects with longer duration ED and with more severe ED, the 50 mg dose was less effective for successful penetration.

Study TA-302 (ED with diabetes) had 390 patients randomised (85% completion, age 30-78 years, 26.9% ≥65 years, 67% hypertension) with a mean time from ingestion to initiation of sexual activity of 53-55 minutes. The primary efficacy results were:

- Successful intercourse (SEP3): Both avanafil treatment groups were superior to placebo with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in % successful intercourse was:
  - 10.5 (27.73) % for placebo
  - 26.2 (33.71) % for 100 mg
  - 32.1 (32.94) % for 200 mg
- Successful penetration (SEP2): Both avanafil treatment groups were superior to placebo with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in % successful penetration was:
  - 5.9 (31.16) % for placebo
  - 21.5 (37.19) % for 100 mg
  - 22.0 (35.00) % for 200 mg

- IIEF EF domain score: The change was greater in both avanafil treatment groups compared to placebo, with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was:
  - 1.8 (6.24) for placebo
  - 4.6 (7.00) for 100 mg
  - 5.3 (7.50) for 200 mg

Secondary efficacy endpoints were mostly supportive and noting there was a significant improvement in the ability to achieve an erection in the avanafil 200 mg group compared to placebo, but not in the 100 mg group and the percentage of subjects who would use the treatment again was 27% for placebo, 47% for 100 mg and 57% for 200 mg. There was no difference in efficacy by type of diabetes or duration of diabetes.

Study TA-303 (ED following bilateral nerve-sparing radical prostatectomy) had 298 patients randomised (85% completion, age 40-70 years, 16.1% ≥65 years, 42% hypertension). The primary efficacy results were:

- Successful intercourse (SEP3): Both avanafil treatment groups were superior to placebo with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in % successful intercourse was:
  - 4.8 (19.89) % for placebo
  - 18.3 (30.18) % for 100 mg
  - 21.1 (31.83) % for 200 mg
- Successful penetration (SEP2): Both avanafil treatment groups were superior to placebo with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in % successful penetration was:
  - -0.4 (21.59) % for placebo
  - 15.3 (32.21) % for 100 mg
  - 20.8 (31.78) % for 200 mg
- IIEF EF domain score: The change was greater in both avanafil treatment groups compared to placebo, with no significant difference between 100 mg and 200 mg. The mean (SD) change from baseline in IIEF Erectile Function Domain Score was:
  - 0.1 (3.56) for placebo
  - 3.6 (7.04) for 100 mg
  - 5.2 (7.00) for 200 mg

Secondary efficacy endpoints were mostly supportive except there was no difference for the 100 mg group on change in IIEF Orgasmic Function Domain Score and no significant difference between avanafil dose and placebo in the change in IIEF Sexual Desire Domain Score. The percentage of subjects who would use the treatment again was 27.7% for placebo, 39.8% for 100 mg and 57.6% for 200 mg. There was no apparent subgroup effect but the groups were small.

Study TA-501 had 440 patients randomised (80-86% completion, age 24 to 86 years, 29.3% ≥65 years, 54.5% hypertension). The primary efficacy endpoint of proportion of sexual attempts that had an erectogenic effect ≤17minutes following dosing (erection sufficient for vaginal penetration and that enabled satisfactory completion of sexual intercourse) was:

- Mean (SE) erectogenic effect:

- 13.78 (2.905) % for placebo
- 24.71 (2.911) % for 100 mg, p=0.002
- 28.18 (2.876) % for 200 mg, p<0.001, (p=0.33 compared to 100 mg)

Secondary efficacy endpoints were supportive including a significant erectogenic effect from 10 minutes after dosing for both avanafil doses; however there was no significant difference between the 100 mg and 200 mg doses.

Study TA-314 was an open label extension study of the first two studies, up to 52 weeks. All subjects were initiated on 100 mg and dose adjusted as needed with two doses allowed in a 24 h period providing they were 12 h apart. The study included 712 subjects: 493 completed to Week 26 and 153 to Week 52. The age range was 23 to 88 years. At last study visit:

- Proportion of subjects with successful intercourse was 67.7% for avanafil 100 mg and 66.3% for 100 mg and 200 mg combined.
- Proportion of subjects with successful penetration was 83.3% for avanafil 100 mg and 79.4% for 100 mg and 200 mg combined.
- Mean (SD) IIEF Erectile Function Domain score was 22.2 (8.57) for avanafil 100 mg and 22.7 (8.12) for 100 mg and 200 mg combined.

A pooled analysis indicated superior efficacy compared to placebo for avanafil 50 mg, 100 mg and 200 mg, both the 100 mg and 200 mg doses are superior to the 50 mg, there was no significant difference between the 100 mg and 200 mg doses for successful intercourse, successful penetration and IIEF Erectile Function Domain Score.

Safety

There were 2144 subjects exposed to avanafil in the development program, including 644 in Phase I, 360 in Phase II, 1140 in Phase III and 153 subjects exposed to avanafil for ≥ 12 months. There were 426 subjects exposed ≥65 years old. In the pivotal studies, adverse events were more frequent on avanafil than placebo with the 200 mg having the highest frequency in two studies and the 100 mg highest in the other two studies:

a. TA-301: 50/100/200/placebo = 32.5/42.2/38.9/26.1%
b. TA-302: 100/200/placebo = 35.4/32.1/23.8%
c. TA-303: 100/200/placebo = 38.4/45.5/23.0%
d. TA-501: 100/200/placebo = 20.5/27.4/21.0%

Adverse events did not appear to be influenced by age, race, diabetes status or coronary artery disease subgroup. The most common adverse event was headache which was dose dependent, for example Study TA-301: 4.4% on 50 mg, 7.5% on 100 mg and 9.3% on 200 mg. Adverse drug reactions were more common on avanafil than placebo and also dose dependent with the most common being headache (dose dependent), flushing and nasal congestion. There was one unrelated death reported in the four pivotal studies in a patient on avanafil 100 mg. Long term safety profile appeared similar to the pivotal studies with headache, flushing and nasal congestion as most common, serious adverse events in no subjects with avanafil 50 mg, six (0.8%) with 100 mg and five (1.0%) with 200 mg and no deaths reported. Serious adverse events were reported across the studies at low levels: TA-301: one (0.6%) subject in the avanafil 50 mg group (acute myocardial infarction), three (1.9%) in the 100 mg (prostate cancer, gunshot wound, bladder cancer), three (1.9%) in the 200 mg (hypoesthesia, coronary artery disease, infected bites) and two (1.2%) in the placebo (non-cardiac chest pain, depression suicidal); TA-302: SAEs were reported in three (2.4%) subjects in the avanafil 100 mg group (deep vein thrombosis, urinary tract infection, localised infection), four (3.1%) in the 200 mg (pain in

extremity/muscular weakness, angina unstable, pneumonia, bladder cancer) and one (0.8%) in the placebo (spinal compression fracture); TA-303: no serious adverse events; TA-501: SAEs were reported in four (2.7%) subjects in the avanafil 100 mg group (atrial flutter, nephrolithiasis, cerebrovascular accident, acute myocardial infarction/unstable angina), three (2.1%) in the 200 mg group (tendon rupture, dyspnoea/coronary artery disease, atrial flutter/atrioventricular block) and two (1.4%) in the placebo (hypertension/bladder outlet obstruction).

Discontinuations due to adverse events occurred at 1.4% on 50 mg, 2.2% on 100 mg, 2.2% on 200 mg and 1.4% on placebo. Elevations in ALT occurred in some patients with one subject across the double blind cohort studies (which included Study TA-301, Study TA-302 and Study TA-05) reporting ALT>3 x ULN on 200 mg. There were no cases meeting Hy's law criteria. There were no clinically significant abnormalities in renal function or haematology reported during the development program for avanafil. ECG abnormalities were seen in three subjects in Study TA-303 on 200 mg (early repolarisation with non-specific ST segment changes; sinus bradycardia (rate 57) with high lateral ST abnormalities and possible ischemia; borderline rhythm) but none were reported in Studies TA-301 or TA-302. One subject in the long term study had an ECG abnormality. Elevated blood pressure was reported in some patients on avanafil. A PSUR did not report any spontaneous serious ADRs.

Risk management plan

The TGA has accepted the EU Risk Management Plan for Spedra (avanafil), version 4.1, dated 30 June 2013 (data lock point 10 October 2012), with the Australian Specific Annex, version 1.1, dated 1 June 2015.

The following were outstanding matters and should be followed up with the TGA and in the sponsor's Pre-ACPM Response:

- Potential risk of QT prolongation: The RMP evaluator agreed with the clinical evaluator that patients with risk factors for cardiac disease could be more sensitive to the effects of an increased dose of avanafil. The sponsor was initially requested to add 'QT interval prolongation' as a potential risk to the ASA and undertake to give specific consideration to arrhythmia events in the PSURs. The sponsor disagreed with this recommendation and provided a response as to why QTc prolongation is not a potential risk for avanafil. The RMP evaluator considered the matter and accepted the sponsor's response given that the sponsor would still investigate and report related AEs through routine pharmacovigilance activities.

  The sponsor should nevertheless undertake to give specific consideration to arrhythmia events in the PSURs.

Risk-benefit analysis

Delegate's considerations

Efficacy

Avanafil has been investigated in four pivotal studies of 12 weeks duration and one open label extension study up to 52 weeks in adult males with erectile dysfunction (mild-severe ED, mild-moderate ED+diabetes, ED+bilateral nerve-sparing radical prostatectomy) assessing doses of 50 mg, 100 mg and 200 mg administered at least 30 minutes prior to sexual activity or in the last study at ≤ 17minutes. Avanafil at doses of 50 mg, 100 mg and 200 mg was superior to placebo in subjects with mild to severe ED. The 100 mg and 200

mg dose levels were both superior to 50 mg. Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with diabetes mellitus and mild to moderate ED. Avanafil at doses of 100 mg and 200 mg was superior to placebo in subjects with ED following bilateral nerve sparing radical prostatectomy. Avanafil at all doses had rapid onset of action in subjects with no restriction of food intake. Avanafil had superior erectogenic effect ≤ 17 minutes after dosing compared to placebo, and there was no significant difference between the avanafil 100 mg and 200 mg dose levels. A maintenance of effect over a 52 week period appeared to be demonstrated from the first two studies.

Safety and RMP

Avanafil has been studied across a range of subjects with ED with an acceptable safety profile and exposure that just exceeds the long term exposure requirements for 12 months. As a PDE5 inhibitor it demonstrates a similar safety profile to other PDE5 inhibitor drugs. Dose related risks of headache, flushing and nasal congestion were most common and serious adverse events occurred at a low level. There was one unrelated death in the pivotal studies and discontinuations showed no clear pattern. An acceptable RMP has been provided and the sponsor has been requested to give specific consideration to arrhythmia in the PSURs.

The evaluator raised concerns about the clinical benefit of the 200 mg dose and associated dose proportionality of adverse events with higher dosage and concerns regarding potential for QT prolongation which led to the recommendation to limit the dose to 100 mg and include a precaution about QT prolongation with overdose into the PI. These matters are discussed further below.

Maximum dose

The clinical evaluator was concerned at the QT prolonging effect of 800 mg avanafil (4 times maximum dose) and whether there could be a potential for QT prolongation at the 200 mg dose (not investigated, but 100 mg was acceptable). The clinical efficacy advantage of the 200 mg dose over the 100 mg dose was not clear and there were more adverse effects at the higher dose. The evaluator commented that ED is not associated with significant morbidity or reduced life expectancy and therefore the risks of approving the 200 mg dose were greater than the benefits and therefore the evaluator recommended rejection of the 200 mg dose. The sponsor responded to this recommendation stating that in all four pivotal trials, the 200 mg dose showed a numerically higher IIEF-EF domain score than the 100 mg and that percentage of subjects with normalised IIEF-EF domain scores (≥26) in trials TA-301, TA-302 and TA-303 were higher on 200 mg than 100 mg (see table below).

Table 7: Normalised IIEF-EF score across studies

Normalised IIEF-EF Score	Mild ED		Moderate ED		Severe ED	
Study	100	200	100 mg	200 mg	100 mg	200 mg
TA-301	17,8%	19,2%	14,0%	15,4%	9,6%	10,3%
TA-302	6,3%	7,1%	6,3%	11,9%	4,8%	4,0%
TA-303	4,3%	7,3%	3,2%	4,2%	5,3%	6,3%

Other parameters of SEP2 and SEP3 also showed numerical differences between 200 mg and 100 mg but were also not statistically significant. However the trials were not designed as such to demonstrate a significant difference between the 100 mg and 200 mg

strengths. In the open label extension study, where patients could up or down titrate, the sponsor states that 'approximately 66% of patients responded to the Avanafil 100-mg dose, and, of those who did not, approximately 65% (112/172) responded to Avanafil 200 mg, for an overall response rate of 75%.' A difference was also seen between 100 mg and 200 mg in the SEP3 score for subjects treated with at least 4 doses of 100 mg and 200 mg. From a safety perspective, the four pivotal trials showed numerically higher percentages of headache (10.2 versus 5.07%, p=0.0015), flushing (4.28 versus 3.38%) and nausea (0.93 versus 0.56%) on the 200 mg versus 100 mg but drug discontinuations due to treatment emergent adverse events were similar on 200 mg and 100 mg (2.04 versus 2.44%). Other than headache, these differences appear to be minor.

The sponsor referred to a Phase IV study that has not been evaluated by the TGA that examined the effect of the 200 mg dose on ocular safety. In this study, the sponsor claims there were no serious adverse events or subject discontinuations due to adverse events and there were no safety concerns with regard to ocular assessments of visual acuity, pupillometry, colour vision discrimination and IOP evaluations. The submission of this study for evaluation will be a condition of registration.

Post-marketing data from 2.7 million therapeutic cycles with the 200 mg dose identified 86 cases of adverse drug reactions on 200 mg (173 cases on 100 mg) with the most common events being headache (11 cases on 200 mg versus 7 cases on 100 mg) and flushing (9 cases on 200 mg versus 11 on 100 mg). Two PSURs were also submitted (period 21 December 2013 to 20 June 2014 and 21 June 2014 to 20 December 2014) with no new safety concerns identified (see agenda papers). The US, EU and New Zealand have all approved a 200 mg dose. Overall, the Delegate is inclined to accept the sponsor's response to approve the 200 mg dose. ACPMs advice is requested on this matter.

Potential for QT prolongation

The nonclinical data did not appear to indicate a potential risk of QT prolongation however the clinical and RMP evaluators raised concerns. A Thorough QT study did not demonstrate a significant effect on the QT interval at the 100 mg dose but an 800 mg dose (4 times the proposed maximum dose) at 3 h (beyond T_{max}) had an upper bound of the 90% CI of 10.2 ms, which is greater than the threshold of regulatory concern (>10 ms). This was based on the pre-specified QTcI (individual correction) and not the QTcF correction which provides a better correction in relation to higher heart rates. More adverse events were noted in the 800 mg group however there were no concerning changes in vital signs or safety ECGs or prolongation of the QT interval over 500 ms. The clinical data have not indicated any cases of ventricular tachycardia (VT) or ventricular fibrillation (VF) in any of the studies. When the sponsor responded with corrections based on QTcB and QTcF, it demonstrated most upper CI intervals exceeded 10 ms on the 800 mg dose (100 mg dose acceptable) based on the QTcB analysis. For the QTcF corrections, only one time point at 3 h showed the upper CI limit >10 ms on the 800 mg dose (100 mg acceptable) which is similar to the original QTcI analysis. The clinical evaluator was concerned at the implications of this for the 200 mg dose, particularly if used with medications that inhibit CYP3A4 and increase avanafil exposure, or in men with other cardiac risk factors, or using drugs that also increase the QT interval.

No Thorough QT study was conducted using a 200 mg dose and thus there is some uncertainty with a signal at 800 mg and a lack of data at the 200 mg dose. The sponsor responded to these concerns stating '*The QTc response of transient prolongation after dosing of Avanafil is consistent with findings of other PDE5 inhibitors, such as vardenafil or sildenafil and has been shown to be related to the change in autonomic state due to sustained reduction in blood pressure followed by compensatory reflex tachycardia rather than due to impaired repolarization*.' This was based on a beat-to-beat analysis from the Thorough QT study that was conducted that assessed avanafil at doses of 100 mg and 800 mg. '*During peak periods of drug concentration from 1 to 4 h, avanafil showed only a slight 1.4% increase*

in the maximum placebo-adjusted % of outlier beats after 100 mg and only 3.4% after 800 mg. This was less than the 9.9% observed at the reported Tmax for moxifloxacin.' '*In summary, the PDE-5 mechanism of action of avanafil, like vardenafil and sildenafil, produces vasodilation, acute reduction in blood pressure, and a compensatory reflex tachycardia. These autonomic changes result in changes to the QT-RR interval relationship, and apparent QTc elevations. Although these changes may transiently exceed the QT interval upper 90% CI threshold of 10 msec for a positive E14 TQT study, the beat-to-beat analyses of all these compounds demonstrate that the % of beats exceeding the normal QT interval 97.5% reference bounds (i.e., the % outlier beats) is not increased and within normal physiological boundaries, mitigating the concern for potential impairment of cardiac repolarization*.'

The sponsor claims that a lack of a significant increase in QTbtb outliers supports the absence of an adverse effect on cardiac repolarisation. The sponsor also states that extensive post-marketing data collected confirm no evidence of an avanafil drug effect on QT interval or cardiac repolarization. Based on an estimated 5 million therapeutic cycles, only one case of serious unspecified arrhythmia occurred in the USA (71 year old male with abnormal ECG finding six days after starting avanafil who was suggested to have a viral cardiomyopathy) that was not considered related to avanafil. The sponsor further advised that '*neither EMA nor FDA have seen fit to include warnings or cautionary statements in the product labelling related to QT prolongation'*. The RMP evaluator agreed with the clinical concerns but following subsequent correspondence from the sponsor has accepted not adding it as a potential risk to the RMP but instead requested that the sponsor give specific consideration to arrhythmia events in the PSURs.

The sponsor has included the results of the QT study in the *Pharmacology* section of the PI, which is consistent with other PDE5 inhibitors, but is not proposing to also include a precaution in the PI consistent with their approved PI in USA, EU and NZ. Overall, the Delegate is inclined to accept the sponsor's response however noting that the vardenafil PI includes a precaution about QT. ACPMs advice is requested on this matter.

200 mg strength tablet

Absorption was faster with the 50 mg tablet strength compared to the 200 mg tablet strength (median T_{max} 0.5 h compared to 0.75 h respectively) and the 200 mg strength tablet was only investigated in the open label extension study, not the pivotal studies. The clinical evaluator was concerned about a lack of investigation of this strength and the delay in T_{max} with the 200 mg strength which may delay onset of effect. However the delay in T_{max} is minor (15 minutes) compared to the 50 mg strength and it has been investigated in the open label extension study, therefore this is unlikely to be clinically significant.

Data deficiencies and limitations

- A lack of data on the potential for QT prolongation at a 200 mg dose.
- Limited data in patients >70 years of age.
- Lack of data in patients on treatment for premature ejaculation or subjects taking illicit drugs.

Conditions of registration

The following are proposed as conditions of registration and the ACPM and sponsor are invited to comment:

1. The implementation in Australia of the EU Risk Management Plan for Spedra (avanafil), version 4.1, dated 30 June 2013 (data lock point 10 October 2012), with the Australian Specific Annex, version 1.1, dated 1 June 2015 and Pre-ACPM Response of [date], included with submission PM-2014-02782-1-3, and any subsequent revisions, as agreed with the TGA.

2. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as Category 1 submission:

    a. Study TA 402: assess the effect of 200 mg avanafil on visual acuity, pupillometry, colour vision discrimination, and intraocular pressure (IOP) in healthy male volunteers.

    b. Study TA 401: assess the effect of daily treatment with avanafil 100 mg on spermatogenesis over a period of 26 weeks.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Please advise of any post approval commitments made with overseas regulatory agencies in regard to the potential for QT prolongation, for example further studies, and whether the sponsor is undertaking any further analyses on this matter or has any further data. The sponsor is also requested to advise whether specific consideration will be given to arrhythmia events in the Periodic Safety Update Reports (PSURs) as requested by the RMP evaluator.

The sponsor is requested to respond to the RMP evaluator's request that all the serious adverse events related to recreational use and off-label use of avanafil should be reported in the PSURs.

Summary of issues

The primary issues with this submission are as follows:

1. Whether the maximum dose should be limited to 100 mg daily.
2. The potential for QT prolongation.

Proposed action

The Delegate had no reason to say, at this time, that the application for Spedra should not be approved for registration. The Delegate's suggested indication is as follows:

Treatment of erectile dysfunction in adult males

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Has acceptable evidence been provided to support the safety and efficacy of a 200 mg dose or should the maximum daily dose be limited to 100 mg?
2. Does the PI require a precaution or other statement in relation to QT prolongation?
3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application

Response from sponsor

Overall recommendation

The sponsor agrees with the Delegate on the recommendation for the approval of Spedra registration (Avanafil 50, 100 and 200 mg tablets) for the '*Treatment of erectile dysfunction in adult male*s', considering that all the relevant primary issues have been duly addressed with the submission of response document to *Second round Clinical and RMP*

Evaluation Reports. Just for completeness the sponsor provides below, a summary of the issues raised by the evaluators and the sponsor position.

- The first concern was about the safety and efficacy of the 200 mg dosage.

With regards to efficacy**,** the sponsor explained that in all four pivotal trials the 200 mg dose demonstrated a numerically higher IIEF-EF domain score than the 100 mg, and that percentage of subjects with normalised IIEF-EF domain scores (≥ 26) in trials TA-301, TA-302 and TA-303 were higher on 200 mg than 100 mg (see Table 7 above), suggesting a better efficacy of 200 mg in restoring the normal erectile function.

In addition, other parameters of SEP2 and SEP3 showed analogous numerical differences between 200 mg and 100 mg. The fact that the differences in results were not statistically significant from those of Avanafil 100 mg can be explained as the studies were not designed to demonstrate a significant difference between individual doses of active drug.

Nevertheless, a more meaningful evaluation of the differences between the 100 mg and 200 mg doses of Avanafil for individual patients was made from the open label extension study (TA-314), where patients were initially assigned to Avanafil 100 mg and could request up-titration to 200 mg or down-titration to 50 mg. During this study, 75% of patients requested an increase in Avanafil dose from 100 mg to 200 mg and experienced additional mean improvement in erectile function as measured by the primary end points.

Approximately 66% of patients responded to the Avanafil 100 mg dose, and, of those who did not, approximately 65% (112/172) responded to Avanafil 200 mg, for an overall response rate of 75%. A difference was also seen between 100 mg and 200 mg in the SEP2 and SEP3 score for subjects treated with at least 4 doses of 100 mg and 200 mg.

From a safety perspective, the profile of Avanafil has been established in 2,144 subjects exposed to the drug during the clinical development program. Considering only the pivotal trials with a common shared design (TA-301, TA-302, TA-303 and TA-501), the total number of TEAEs was not statistically different between the 100 mg and 200 mg dosage.

Looking at the most common specific adverse events (most relevant categories), a statistical difference in favour of 100 mg was found only for the headache category (see Table 8 below). It should also be noted that drug discontinuation due to treatment emergent adverse events were similar on the 200 mg versus 100 mg tablet dosage forms.

Table 8: Treatment-emergent adverse events

	100 mg		200 mg		p-value
Any TEAE	181	33,90%	190	35,30%	P = 0,641
Headache	27	5,07%	55	10,20%	p = 0,0015
Back Pain	9	1,69%	7	1,30%	p = 0,601
Flushing	18	3,38%	23	4,28%	p = 0,444
Nausea	3	0,56%	5	0,93%	p = 0,486
Study drug discontinuations due to TEAEs	13	2,44%	11	2,04%	p = TBD

Sources: *CSR TA-301, CSR TA-302, CSR TA-303, CSR TA-501*

Also the post-marketing experience on approximately 2.7 million therapeutic cycles with Avanafil 200 mg up to December 2014 (calculated on the basis of internal sales data, taking into account a therapeutic cycle is a patient taking 1 tablet of Avanafil) confirmed the positive benefit/risk profile of the 200 mg dosage.

The sponsor would like to point out also that, according to *EAU 2015 Guidelines on Erectile Dysfunction and Premature Ejaculation*, Avanafil 200 mg appears to be the safest in the class of marketed PDE 5 inhibitors, thereby confirming that Avanafil, from 50 to 200 mg, is effective and well tolerated for the treatment of ED, and that an increase in dosage is associated with a significant rise in efficacy, but with no significant increase in AEs.

Table 9: Frequency of adverse events reported for 200 mg Avanafil versus Sildenafil, Tadalafil and Vardenafil

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon
Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	none
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Finally, as also detailed in the following paragraph, the sponsor would like to confirm that Study Report TA 401 and TA 402 will be submitted for evaluation as Category 1 submission after approval as per the proposed Conditions of registration.

In conclusion, the sponsor considers that the benefit/risk profile of both the 100 mg and the 200 mg is positive with the dosage of 200 mg being a potential benefit for an important number of ED patients.

- Another concern raised by the clinical and RMP evaluators was the potential of Avanafil for prolongation of QT interval, thereby proposing the insertion of a precaution in the PI (Overdosage section) and RMP (as a Potential risk), even if the non-clinical data did not appear to indicate such potential risk.

The sponsor responded to this issue stating that the QT interval has been deeply discussed and analysed during different registration procedures and has not been considered by different regulatory authorities (like EMA and FDA) as a potential risk for Avanafil.

In particular, the sponsor submitted the results of a thorough QT/QTc study (TA-140). The primary objective of this study was to assess whether treatment with a therapeutic (100 mg) or supratherapeutic (800 mg) dose of Avanafil had the potential to cause QT/QTc prolongation in healthy volunteers.

From the study, the sponsor has obtained different QT analyses using the Bazzet, Fridericia, QTcI (individual) and (as required by FDA) beat-to-beat (QTbtb) algorithms for correction of the effects of heart rate on observed QT intervals, all demonstrating that Avanafil exhibited no true drug effect of clinical or regulatory concern on the QT interval or cardiac repolarisation. In particular the beat-to-beat analyses demonstrated that the % of beats exceeding the normal QT interval 97.5% reference bounds (that is, the % outlier beats) is not increased and within normal physiological boundaries, mitigating the concern for potential impairment of cardiac repolarisation. Also the data collected in the extensive post-marketing experience confirm no evidence of an Avanafil drug effect on QT interval or cardiac repolarisation.

In conclusion, the sponsor agrees with the final position of RMP evaluator confirming not to add QT prolongation as a potential risk to the AU RMP. Furthermore the sponsor confirms that, as requested by the RMP evaluator, specific considerations to any arrhythmia events will be provided in the next PSURs, by investigating them through routine pharmacovigilance activities.

Data deficiencies and limitations

Issues raised*:*

1. A lack of data on the potential for QT prolongation at a 200 mg dose.
2. Limited data in patients >70 years of age.

3. Lack of data in patients on treatment for premature ejaculation or subjects taking illicit drugs.

Sponsor comment

1. The sponsor acknowledges the first remark but at the same time would like to specify that the 200 mg dose was investigated in Study TA-314 which was an open-label extension of Study TA-301 and Study TA-302 to evaluate the long-term safety, tolerability and efficacy of Avanafil in men with mild to severe ED. The study included subjects who had completed Study TA-301 and Study TA-302 and the following study treatments were investigated:

   Avanafil 50 mg tablet, Avanafil 100 mg tablet and Avanafil 200 mg tablet.

   In the study, 712 patients were enrolled and about 75% of subjects requested that their dose of Avanafil be increased and thus received both Avanafil 100 mg and 200 mg. Therefore, a total of 536 subjects were treated with the high dose of Avanafil 200 mg and no clinically important safety findings were noted from the summary of changes in safety laboratory parameters or ECG parameters or physical examination findings at the end of treatment. Furthermore, mean SBP, DBP, and heart rate values at the end of treatment were similar to those at enrolment.

   Avanafil treatment demonstrated significant improvements in erectile function assessments and was not associated with any notable safety concerns or QT prolongation. The efficacy and safety results of this study, as well as the extensive post-marketing experience, indicate a very favourable benefit/risk profile for Avanafil, with no evidence of an Avanafil drug effect on QT interval or cardiac repolarisation even at a higher dose (200 mg). Nevertheless, as confirmed in the section below (*Questions for the sponsor*), arrhythmia events will be monitored in the upcoming PSURs.

2. The sponsor acknowledges the comment, and has amended the Product Information accordingly.

3. The sponsor acknowledges the comment, and would like to remark that this missing information is duly reflected in the proposed Product Information (Section 'Precautions' – *[…] The use of Avanafil with illicit drugs has not been studied*). Furthermore, as stated in the section '*Questions for the sponsor*', the sponsor would like to highlight that all the serious AEs related to recreational use and off-label use of Avanafil will be duly monitored and reported in the upcoming PSURs.

Conditions of registration

1. The implementation in Australia of the EU Risk Management Plan for Spedra (Avanafil), version 4.1, dated 30 June 2013 (data lock point 10 October 2012), with the Australian Specific Annex, version 1.1, dated 1 June 2015 and Pre-ACPM Response of [date], included with submission PM-2014-02782-1-3, and any subsequent revisions, as agreed with the TGA.

Sponsor comment

The sponsor acknowledges TGA's request and would like to confirm that the Risk Management Plan for Spedra in Australia will be implemented according to the last revisions as agreed with the TGA.

2. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as Category 1 submission:

   – Study TA 402: assess the effect of 200 mg Avanafil on visual acuity, pupillometry, colour vision discrimination, and intraocular pressure (IOP) in healthy male volunteers.

– Study TA 401: assess the effect of daily treatment with Avanafil 100 mg on spermatogenesis over a period of 26 weeks.

Sponsor comment

The sponsor acknowledges the request and would like to highlight that both studies are completed and the dataset will be submitted for evaluation after the current Category 1 application is approved.

Question for the sponsor from the delegate

1. Please advise of any post approval commitments made with overseas regulatory agencies in regard to the potential for QT prolongation, for example further studies, and whether the sponsor is undertaking any further analyses on this matter or has any further data. The sponsor is also requested to advise whether specific consideration will be given to arrhythmia events in the PSURs as requested by the RMP evaluator.

Sponsor comment

The sponsor would like to advise that an additional study evaluating the QTc prolongation of Avanafil was under discussion with EMA since the product registration. EMA concurred with the sponsor that such further evaluation would not provide meaningful insight for the QT prolongation risk, considering what was already provided in the course of the initial MAA assessment (that is, Study TA-140 and all the different QT analyses). EMA requested to include in the next PSUR a statement with the arguments presented in order to close the discussion.

The request was endorsed with the last PSUR (#4 - From 21 December 2014 to 21 June-2015) submitted to EMA on 28 August 2015.

Thus the Marketing Authorisation Holder (MAH) position has now been accepted by EMA, and therefore the sponsor can confirm that there is no pending post-approval commitment with overseas regulatory agencies in regard to the potential for QT prolongation. Furthermore, the sponsor confirms that specific consideration will be given to arrhythmia events in the next Periodic Safety Update Reports (PSURs).

2. The sponsor is requested to respond to the RMP evaluator's request that all the serious adverse events related to recreational use and off-label use of Avanafil should be reported in the PSURs.

Sponsor comment

The sponsor hereby confirms that all the serious adverse events related to recreational use and off-label use of Avanafil will be duly monitored and reported in the next PSURs.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Spedra uncoated tablet containing 50 mg, 100 mg and 200 mg of avanafil to have an overall positive benefit–risk profile for the Delegate's amended indication**;**

Treatment of erectile dysfunction in adult males.

In making this recommendation the ACPM;

- Was of the view that the 200 mg tablet should be registered as it appeared to be efficacious in patients with diabetes.

- Noted that there was limited evidence of use in patients over 70 years of age and that avanafil was not studied in patients with severe chronic kidney disease.
- Expressed concern over the use of the QT beat to beat analysis, noting that it is not routinely used in the clinical setting.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Under *Overdosage*, a warning about the potential for QT prolongation and lack of information on the potential for a QT effect at the 200 mg dose.
- Include a statement that the additional efficacy of the 200 mg dose seems to be limited.
- Under *Precautions*, *Concomitant use of alpha blockers*, specify the active ingredients names for alpha blockers, such as prazosin, tamsulosin, terazosin etc, to improve clarity for prescribers.
- Under *Use in Elderly*, the PI should state that data on patients older than 70 years are limited as there were very few patients in this age group included in the trials.
- Reinforce the statements on use and efficacy of avanafil in chronic kidney failure, since there are very little data in patients with eGFRs[17] less than in the clinical trials.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Has acceptable evidence been provided to support the safety and efficacy of a 200 mg dose or should the maximum daily dose be limited to 100 mg?*

The ACPM noted that for most of the populations studied there was no significant difference in effect between the 100 mg and the 200 mg dosage of avanafil. However, in patients with diabetes, there was a significant improvement in the ability to achieve an erection in the avanafil 200 mg group compared to placebo, but not in the 100 mg group. The ACPM was of the view that patients would possibly take a dose of 200 mg, which would be of limited benefit in most patients and noted that the 200 mg tablet was registered in other jurisdictions. The ACPM advised that the daily dose should not be limited to 100 mg. However, the PI should clearly state that the additional benefit of the 200 mg dose seems to be limited.

2. *Does the PI require a precaution or other statement in relation to QT prolongation?*

The ACPM expressed concern over the use of the QT beat to beat analysis, noting that it is not routinely used in the clinical setting and that there was no justification for its use in the pre-study specification. Therefore, the result on QT interval for the 800 mg dosage could not be considered spurious. The ACPM noted that that it is unknown what percentage of heart beats in a patient with long QT syndrome over a 24 h period express a significantly prolonged interval. It therefore remains unknown what percentage there would need to be to reflect risk.

[17] eGFR=estimated glomerular filtration rate

The ACPM advised that the PI did require a statement regarding QT prolongation, particularly in overdose and suggested the statement outlined above in *Proposed PI/CMI amendments.*

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Spedra avanafil 50 mg tablet blister pack, Spedra avanafil 100 mg tablet blister pack, Spedra avanafil 200 mg tablet blister pack for oral administration for the indication:

Treatment of erectile dysfunction in adult males.

Specific conditions of registration applying to these goods

1. The avanafil EU-Risk Management Plan (RMP), version 4.1, dated 30 June 2013 (data lock point 10 October 2012), with the Australian Specific Annex, version 1.1, dated 1 June 2015 and Pre-ACPM Response of September 2015, included with submission PM-2014-02782-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
2. The following study reports must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category I submission(s):
    i. Study TA 402: assess the effect of 200 mg avanafil on visual acuity, pupillometry, colour vision discrimination, and intraocular pressure (IOP) in healthy male volunteers.
    ii. Study TA 401: assess the effect of daily treatment with avanafil 100 mg on spermatogenesis over a period of 26 weeks

Attachment 1. Product Information

The PI for Spedra approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au