Taiwan Food and Drug Administration

Assessment Report

Trade Name：Spedra tablet 50, 100, 200 mg

Active Ingredient：Avanafil

License Number：MOHW-PI 028081, 028082, 028083

Applicant：新加坡商美納里尼醫藥有限公司台灣分公司

Approval Date：2021/05/23

Indication：治療成年男性勃起功能障礙。
Spedra is used to treat adult men with erectile dysfunction.

Background Information

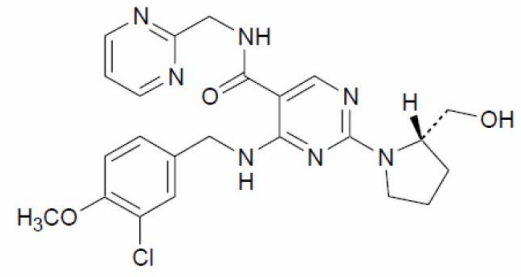
Trade Name	Spedra 50, 100, 200 mg tablet
Active Ingredient(s)	Avanafil
Applicant	新加坡商美納里尼醫藥有限公司台灣分公司
Dosage Form & Strengths	Tablets 50, 100, 200 mg
Indication	治療成年男性勃起功能障礙。 Spedra is used to treat adult men with erectile dysfunction.
Posology	起始劑量為 100 毫克，於性行為前約 15 至 30 分鐘視需要服用。依據病人個別療效和耐受性，最高劑量可增加至 200 毫克，或降低至 50 毫克。服藥最多每天一次。治療要產生反應，性刺激是必須的。 The recommended starting dose is 100 mg, taken approximately 15 to 30 minutes as needed before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to 200 mg, or decreased to 50 mg. The maximum recommended dosing frequency is once per day. Sexual stimulation is required for a response to treatment.
Pharmacological Category **ATC Code**	G04BE10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, avanafil, is chemically designated as 4-[(3-chloro-4-methoxybenzyl) amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide. The chemical structure of avanafil is shown below:



It is a white to almost white powder. The molecular formula and the molecular weight are

$C_{23}H_{26}ClN_7O_3$ and 483.95 g/mol, respectively.

Adequate information of characterization of the drug substance has been provided. The specification of the drug substance includes tests for appearance, identification, assay, related substances, volatile impurities and inorganic impurities.

2.1.2 Drug product

The drug product is supplied for oral administration with three strengths that contain 50 mg, 100 mg and 200 mg of avanafil.

The excipients used in the drug product formulation comply with the compendial monographs.

The specification of the drug product includes appearance, identification, assay, purity, uniformity of dosage unit, dissolution and microbial enumeration tests. Analytical methods are described well and validated.

Stability studies of the drug product under long term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Avanafil is a potent inhibitor of the cGMP-specific phosphodiesterase 5 (PDE5). In the erectile tissues, PDE5 is responsible for cGMP degradation. Mechanism-wise, in men, sexual stimulation causes nerves and endothelial cells to release nitric oxide (NO), which diffuses into smooth muscle cells of penile arteries and spongy tissues. NO dilates smooth muscle cells by increasing intracellular cGMP levels and subsequently increases blood flow into the penis. Through inhibition of PDE5 in the erectile tissues, the cGMP level is maintained or even higher and results in enhanced smooth muscle relaxation and erectile response.

In vitro, avanafil was highly selective against PDE5 among PDE isoforms. The IC50 value for avanafil at PDE5 is similar to those for the other marketed PDE5 inhibitors for erectile dysfunction. Notably, compared to sildenafil and vardenafil, avanafil displayed low activity at PDE6, which is considered responsible for visual disturbances observed in some patients treated with sildenafil. Avanafil had been shown its efficacy in isolated rabbit tissue and in vivo rabbit, dog, and monkey ED models, in which the potentiation of the stimulation-induced penile tumescence in a dose-dependent manner was demonstrated. Avanafil did not exhibit significant affinity for a series of enzymes and receptors, including nitric oxide synthases. Compared to sildenafil, avanafil showed a good selectivity profile to adenosine and $\alpha 1$ adrenergic receptor.

Safety pharmacology studies generally indicated that avanafil had minimal effects on the central nervous, respiratory and cardiovascular systems in rats and dogs. Avanafil had been shown to inhibit hERG current in vitro and shorten the action potential's average duration in the isolated canine cardiac Purkinje fibers with the estimated IC50 values 416-fold and more than 2600-fold above the unbound Cmax at MRHD, respectively. Avanafil produced a decrease in blood pressure and increased heart rate in dogs, possibly due to this class of drugs' vasodilatory effects. Except for a tendency of increases in QTc that remained within normal range had been noted in a single-dose toxicology study in dogs, no other noteworthy effects of avanafil on electrocardiography were observed in vivo. In other safety pharmacology studies, including evaluations in the gastrointestinal and genitourinary systems, avanafil was generally inactive or had effects only at relatively high doses. In particular, avanafil had no effects on eye functions noted in dog study. Avanafil potentiated the effects of nitroglycerin in dogs. Therefore, avanafil should be contraindicated in patients taking nitrates due to the risk of potentiation of hypotension.

Single oral administration of avanafil was well tolerated, and no significant adverse effects were shown at doses up to 2000 mg/kg in rats and dogs, except the similar effects on blood pressure and heart rates noted in the safety pharmacology study in dogs. Repeat-dose toxicology studies primarily showed decreased bodyweight, increased liver weight, and hepatocellular hypertrophy, which was indicative of metabolizing enzyme induction. The NOAELs of avanafil were 300 and 30 mg/kg/day in the 26-week rat study and the 9-month dog study, respectively, provided safety margins approx. 9-fold and 36-fold unbound human exposure at MRHD.

Avanafil was negative in all but one genotoxicity assay, the in vitro mouse lymphoma assay, and was negative in two-year carcinogenicity studies in mice and rats. A complete battery of reproductive toxicity studies has been conducted. In rat fertility studies, effects on sperm, with or without accompanying decrease in fertility, were observed at the highest dose tested. Complete reversibility of the effects on sperm had been demonstrated following the recovery period. An embryofetal development study in rats produced maternal toxicity at the highest dose tested with a decrease in fetal body weight but no increase in fetal malformations or variations. In pregnant rabbits, maternal toxicity was evident at the highest dose tested without developmental toxicity or an increase in the incidence of fetal malformations observed. In a rat pre- and post-natal development study, decreases in offspring body weight and weight gain were reported at doses equal to or below the dose produced maternal toxicity, with corresponding slight delays in sexual maturation at the highest dose tested. No other findings in developmental or reproduction performance in the offspring were noted. Lastly, avanafil showed no phototoxicity to pigmented rats.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Avanafil is rapidly absorbed after oral administration, with a median T_{max} of 30 to 45 minutes in the fasted state. There was little or no accumulation observed after once daily administration. High fat meal decreased the C_{max} of avanafil and delay the T_{max} (form 0.75 hr to 2 hr). Because AUC of avanafil was not affected by high fat meal, avanafil can be administered with or without food.

The plasma protein binding of avanafil is approximately 99%, and the binding ratio is independent of total drug concentrations, age, renal and hepatic function. Following the administration of one 200 mg avanafil tablet in young male subjects, less than 0.0002% of the administered dose appeared in the semen of subjects. Avanafil is cleared predominantly by hepatic metabolism, mainly by the CYP3A4 and to a minor extent by CYP2C isoform. M4 (active metabolite) and M16 (inactive metabolite) were the two major circulating metabolites. The terminal elimination half-life of avanafil is approximately 5 hours.

2.3.2 Interaction Studies

Co-administration of avanafil with strong CYP3A4 inhibitor is contraindicated due to significant elevation of the exposure of avanafil. A moderate CYP3A4 inhibitor also increased the exposure of avanafil about 2-fold to 3-fold when combined these two drug. Thus, the maximum recommended dose of avanafil is 50 mg, not to exceed once every 24 hours. If avanafil is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating treatment with avanafil, and avanafil should be initiated at the 50 mg dose. Concomitant use of nitrates in any form is contraindicated. Also, other drugs which have potential of hypotensive effects should be pay attention when coadministration of them, more detailed information was stated in labeling.

2.3.3 Special Populations

The exposure of avanafil was similar between healthy young (18 - 45 years) and healthy elderly (65 year or older) male subjects. Thus, no dose adjustment is needed for avanafil based on age. No dose adjustment is required in mild to moderate renal impairment (creatinine clearance $\geq$ 30 to <80 mL/min) because the exposure of avanafil did not have significant difference and the renal excretion was not the major route of elimination of avanafil. The exposure (C_{max} and AUC) of avanafil between patients with mild hepatic impairment (Child-Pugh Class A) and healthy subjects were similar.

The C_{max} of avanafil in patients with moderate hepatic impairment (Child-Pugh Class B) were lower (↓57%) than those in healthy subjects, but AUC_{inf} of avanafil between them were comparable. No dose adjustment is necessary for patients with mild to moderate hepatic

impairment (Child Pugh Class A or B). Avanafil is contraindicated in patients with severe renal impairment and severe heaptic impairment due to lack of data.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Three Phase III, double-blind, multi-center, placebo-controlled studies ([TA-301], [TA-302], and [TA-303]) have been provided to support the efficacy of Spedra (avanafil) for the treatment of erectile dysfunction (ED) in men. In Study [TA-301], three Avanafil doses (50 mg, 100 mg, and 200 mg) were administered in general ED population, while in Studies [TA-302] and [TA-303], two doses (100 mg and 200 mg) were administered in diabetic subjects and in subjects following bilateral nerve-sparing radical prostatectomy, respectively.

The same co-primary efficacy endpoints, used for all three studies, are:

- 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 (SEP3)
- 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 (SEP2)
- Change in IIEF EF domain score from baseline to end of the 12-week treatment period (IIEF EF Domain Score)

The main efficacy results are summarized in Table 2.4.1. The data from the three Phase III studies demonstrated that all three avanafil doses (50 mg, 100 mg, and 200 mg) have statistically significant improvement in the three pre-specified co-primary endpoints compared with placebo. The treatment effects of avanafil 100 mg and 200 mg are statistically significantly more effective than avanafil 50 mg on all three co-primary endpoints. Although in these three studies, avanafil 200 mg is not more effective than avanafil 100 mg on any co-primary endpoint, its numerical benefit was observed.

Table 2.4.1 LS mean difference (p-value) for the co-primary endpoints in each pivotal study

Treatment comparisons	Successful Intercourse (SEP3)	Vaginal Penetration (SEP2)	IIEF EF Domain Score
Study [TA-301]			
Avanafil 200 mg vs. placebo	30.2% (< 0.0001)	22.7% (< 0.0001)	6.7 (< 0.0001)
Avanafil 100 mg vs. placebo	29.3% (< 0.0001)	20.1% (< 0.0001)	5.5 (< 0.0001)
Avanafil 50 mg vs. placebo	13.8% (0.0002)	11.1% (0.0009)	2.6 (0.0014)
Avanafil 200 mg vs. Avanafil 50 mg	16.4% (< 0.0001)	11.7% (0.0004)	4.1 (< 0.0001)
Avanafil 100 mg vs. Avanafil 50 mg	15.6% (< 0.0001)	9.0% (0.0064)	2.9 (0.0003)
Avanafil 200 mg vs. Avanafil 100 mg	0.8% (0.8198)	2.6% (0.4221)	1.2 (0.1366)
Study [TA-302]			

Avanafil 200 mg vs. placebo	20.4% (< 0.0001)	18.4% (< 0.0001)	3.6 (< 0.0001)
Avanafil 100 mg vs. placebo	15.2% (< 0.0001)	14.0% (0.0004)	2.8 (0.0017)
Avanafil 200 mg vs. Avanafil 100 mg	5.3% (0.1724)	4.4% (0.2719)	0.8 (0.3387)
Study [TA-303]			
Avanafil 200 mg vs. placebo	15.6 % (< 0.0001)	20.1% (< 0.0001)	5.0 (< 0.0001)
Avanafil 100 mg vs. placebo	14.2% (0.0004)	14.8% (0.0003)	3.5 (0.0001)

In conclusion, there is sufficient evidence to support the efficacy of avanafil (50 mg, 100 mg, and 200 mg) for the treatment of erectile dysfunction in men.

2.4.2 Safety Results

The integrated safety analyses include data from the three Phase 3 double-blind studies (TA-301, TA-302 and TA-303) and the Phase 2 double-blind study (TA-05). These studies were similar with respect to study population (mild to severe ED), design, treatment period (12 weeks), dosing instructions (as-needed) and basic visit structure. Subjects from these studies who received avanafil 50 mg, 100 mg, 200 mg, or placebo were included in the ISS.

Overview of Adverse Events

The incidence of TEAEs was higher among the avanafil groups (31.3% to 39.7%) than in the placebo group (24.9%). Most of the TEAEs were mild or moderate in severity. The distribution of TEAEs by maximum severity was similar across treatment groups. The incidence of discontinuation due to TEAE was low: 1.3% in the placebo group, 1.4% to 2.2% in the avanafil group.

The most common (>1%) reported TEAEs among the avanafil groups and with higher incidence than the placebo groups included: Upper respiratory tract infection, influenza, headache, back pain, nasal congestion, sinus congestion, flushing and dyspepsia. The most frequently reported severe TEAE was headache (2 subjects).

The incidence of SAEs among subjects in this safety analysis was low: 0.9% ~ 1.6% of subjects treated with avanafil vs 0.9% of subjects receiving placebo. One subject (in the avanafil 100 mg group, study TA-301) died and this event was judged unrelated.

Targeted Medical Events

The following classes of events related to PDE5 inhibitors were identified as targeted medical events: hemodynamic changes, special sensory effects (vision or hearing), major cardiac events, upper respiratory events and priapism. The incidences of TEAEs categorized as hemodynamic changes, major cardiac events and special sensory effects were low (<1%) and similar for the treatment groups. No subject in this safety analysis had a TEAE of hypotension or priapism.

Clinical Laboratory Evaluations

The numbers and percentages of subjects with abnormal laboratory measurements were low and no meaningful differences among the treatment groups were observed.

Others

The results from the thorough QT/QTc study demonstrated that avanafil does not cause any significant changes in QTc interval or ventricular repolarization over an 8-fold exposure range above an expected therapeutic dose. Single oral doses of avanafil 200 mg administered to healthy male volunteers produced no significant difference compared to placebo in sitting SBP, DBP and pulse rate. The incidences of abnormal change in SBP or DBP in the double-blind ISS were low and similar across the treatment groups. No acute effect on sperm function after a single dose of avanafil 200 mg was observed in young healthy male subjects. While a small percent of the avanafil dose (~0.0002%) was detected in seminal fluid.

2.5 Bridging Study Evaluation

The exposure in Korean male subjects was higher (Cmax:>2-fold; AUC: 2- to 4-fold) than that in non-Asian subjects. No other East Asian PK information can be provided by sponsor. There was no steep relationship between exposure and efficacy or safety. The ethnic difference could not be determined from PK point of view based on limited data.

Spedra® was globally first approved in South Korea. A set of clinical studies were conducted in the Korean population, including a phase 2 study [AVA-201] and two phase 3 studies [AVA-301, AVA-302]. Because the study design of Study AVA-301 was similar to global studies, BSE focused on the results of Study AVA-301.

The efficacy summary of Study AVA-301:

- For primary efficacy endpoint, changes of the scores in IIEF EF Domain scores after 12 weeks compared with baseline indicated statistically significant improvement in all groups, including both avanafil 100mg and 200mg, and the placebo group ($P < 0.05$). As for the changes in the IIEF EF scores from baseline and after the study, both avanafil groups (100mg and 200mg) showed significantly improved results compared to the placebo group (All $P < 0.05$).
- For secondary efficacy endpoints, within the analysis for other domains of IIEF, the scores were significantly improved in both avanafil groups (100mg and 200mg) compared to the placebo group. After 12 weeks of treatment, the result was that both avanafil groups (100mg and 200mg) had significantly higher rate of recovery to normal erectile functions ($P < 0.05$). The other secondary endpoints about SEP Q2, Q3, Q4 and Q5, all showed a statistically significant increase in the success rate in both avanafil groups (100mg and 200mg) compared to the placebo groups ($P < 0.05$). The GEAQ showed significant improvement with both avanafil groups (100mg and

200mg).

The summary on safety of Study AVA-301:

The incidence of TEAEs was higher in the avanafil groups than in the placebo group. However, the majority TEAEs in the avanafil groups were mild to moderate. The incidence of discontinuation due to TEAEs in the avanafil groups was very low. Only one serious adverse drug reaction was reported in the avanafil groups. No death was reported in Study AVA-301.The most commonly reported reactions was flushing and headache. Both of them were below 10% and disappeared without specific treatments.
The laboratory analysis (hematological, biochemical, urinary analysis), and the EKG or other vital signs did not show any clinically relevant differences among the treatment groups.
In summary, both of the avanafil groups (100mg and 200mg) were shown to be safe in Korean patients with erectile dysfunction.

Based on Post-Marketing Safety Surveillance data in Korean (Aug-17-2011 ~ Aug-16-2017), a total of 4,330 subjects was included. 4121 (95.2%) subjects were initially prescribed with Spedra® 200mg. The incidence of AEs was 1.2%. The most commonly reported TEAEs were hot flushing (0.62%) and headache (0.44%). Neither SAE nor death was reported.

In conclusion, no ethnic difference with clinical impact was observed between East Asian subjects and Caucasian subjects from clinical perspective. BSE waive was recommended.

2.6 Conclusion

In conclusion, avanafil as treatment for erectile dysfunction in adult males demonstrates a favorable risk-benefit profile with enough evidence to recommend regular approval.

3. Post-Marketing Requirements

NA