Brand Name: Stendra

Generic Name: avanafil

Manufacturer: Vivus, Inc.[1]

Drug Class: Phosphodiesterase-5 Enzyme Inhibitor[1,2,3,4]

Uses:

Labeled Uses: Treatment of erectile dysfunction (impotence) [1,2,3,4]

Unlabeled Uses: None currently known

Mechanism of Action[1,2,3,4]

Nitric oxide increases levels of cGMP, which relaxes smooth muscles in corpus cavernosum to allow inflow of blood to achieve and maintain penile erection. Avanafil, a selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE-5), enhances the effect of nitric oxide by inhibiting PDE-5, which degrades cGMP in the corpus cavernosum. Sexual stimulation is required to initiate the local release of nitric oxide. Avanafil has no direct relaxant effect on corpus cavernosum

Pharmacokinetics[1,2,3,4]

Absorption:

T_{max} - Fasting - High Fat Meal	 - 30-45 min - 1.12-1.25 hr
V_d	0.058-0.226 ml (Korea)
$t_{½}$	5 hrs
Clearance	0.013-0.025 m/hr (Korea)
Protein binding	99%
Bioavailability	Not Reported

Metabolism: Avanafil is cleared predominantly by hepatic metabolism, mainly by the CYP3A4 enzyme and to a minor extent by CYP2C. The plasma concentrations of the major circulating metabolites, M4 and M16, are approximately 23% and 29% that of the parent compound, respectively. The M4 metabolite has an *in vitro* inhibitory potency for PDE5 18% of that of avanafil and M4 accounts for approximately 4% of the pharmacologic activity of avanafil. The M16 metabolite was inactive against PDE5.

Excretion: After oral administration, avanafil is excreted as metabolites predominantly in the feces (approximately 62% of administered oral dose) and to a lesser extent in the urine (approximately 21% of the administered oral dose)

Efficacy:

Zhao C, Kim SW, Yang DL, et al. Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. BJU International 2012.

Study Design: Multicentre, randomized, double-blind, placebo-controlled, fix-dose phase III clinical trial

Description of Study: *Methods:* Two hundred patients diagnosed with ED for at least 6 months were randomly assigned to receive placebo, 100mg of avanafil, or 200mg of avanafil. Patients were allowed to take the investigational drug when necessary 30 minutes before sexual intercourse but were not to exceed one dose per day. The study consisted of a 12-week treatment period. The primary outcome variable was the change from baseline for IIEF erectile function domain (EFD) scores. The secondary outcome variables were SEP Q2 and Q3 (Sexual Encounter Profile questionnaire), patient responses to the Global Assessment Question (Has the treatment you have been taking during the study improved your erections?), and the percentage of patients exhibiting a 'shift to normal' (IIEF-EFD score > 26). All adverse effects events were monitored, recorded, and assessed for seriousness, intensity, and relationship to the study drug. *Results:* Both the active drug groups showed statistically significant improvement in EFD scores of the IIEF from baseline, while the placebo group did not. The mean changes of EFD scores were 8.5 for the 100mg group and 8.8 for the 200mg group, both of which were significantly greater than the placebo group (3.5). All of the secondary outcomes for the avanafil groups differed significantly from the placebo group. In general, avanafil was safe and well tolerated. Most adverse events were mild or moderate in severity. The most commonly reported treatment-related event was flushing. No significant changes in laboratory tests, electrocardiograms, or blood pressure were observed in the avanafil groups.

Limitations: The study did not evaluate the effects of this medication in different ethnicities. Differences in metabolism between ethnicities may alter the results and side effect profile of this drug. The study excluded patients with prior inadequate response to other PDE5 inhibitors, so it cannot be determined if avanafil could produce a better response in this population. The study also evaluated avanafil compared to placebo, not another PDE5 inhibitor so there is no way to

tell if it is more effective than the current drugs on the market. Many of the outcome variables were subjective measurements based upon each individual patient response to questions. More objective measurements would have provided more solid evidence of the drug effectiveness; however, given the nature of this drug, such objective measures do not exist and the measurements used were the best options available. Larger trials with longer treatment duration and a more diverse patient population are needed to distinguish the safety and efficacy profiles between the different drug strengths.

Conclusion: Avanafil proved to be both safe and effective compared to placebo in the treatment of healthy Korean subjects with mild to severe ED. The adverse effects were similar to those found in other PDE5 inhibiting agents, though further studies in more diverse populations are needed. This new drug could provide another reliable option to be considered for patients with ED.

Jung J, Choi S, Cho SH, et al. Tolerability and Pharmacokinetics of Avanafil, a Phosphodiesterase Type 5 Inhibitor: A Single- and Multiple-Dose, Double-Blind, Randomized, Placebo-Controlled, Dose-Escalation Study in Health Korean Male Volunteers. Clinical Therapeutics. 2010; 32(6):1178-86.

Study Design: Double-blind, randomized, placebo-controlled, parallel-group, dose-escalation study

Description of Study: *Methods:* 32 subjects were randomly allocated to receive 50, 100, or 200 mg tablets of avanafil or placebo once daily for 7 days. Tolerability was assessed by monitoring vital signs and results of laboratory tests, 12-lead ECGs, and color discrimination tests. Blood samples of 6 ml were collected in heparinized tubes before and at varying hours after drug administration on days 1 and 7. Plasma concentrations of avanafil were measured using LC-MS/MS. Pharmacokinetic parameters of avanafil on days 1 and 7 were determined by noncompartmental analysis and compared among the 3 dose groups. *Results:* 30 of the 32 males initially enrolled completed the study. Adverse events were reported by 20 of the 25 (80%) subjects taking avanafil and by 4 of the 6 (67%) taking placebo. None of the events were considered "serious", all resolved spontaneously, and there were no clinically relevant changes in vital signs, ECG, physical exam, or color discrimination results. The drug reached its Tmax at 0.33-0.52 hour after dosing. The apparent mean half life was 5.36-10.66 hours. AUC and Cmax were proportional to the dose, and the mean accumulation index on day 7 after a single daily dose was 0.98.

Limitations: The inclusion and exclusion criteria for this study were too stringent to allow proper extrapolation of the results to the general patient population. Also, the sample size for the various groups were very small. More serious side effects could be determined with a large study size and broader population criteria. Also, the treatment regimen in this study does not portray actual use of the drug in the public. It is supposed to be taken on an as needed basis up to once a day for sexual intercourse, not as a scheduled daily dose. The drug is not shown to be effective without intention of sexual activity.

Conclusion: This study has many limitations and it would be difficult for its results to be applied to a more generalized patient population due to variability of CYP metabolism throughout different races. Much larger studies with greater variability between patients are needed for a more accurate picture of the tolerability of this drug. With that being considered, this drug was shown to be generally well tolerated in this small population and it exhibited a favorable linear kinetic profile with minimal accumulation.

Goldstein I, McCullough AR, Jones LA, et al. A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Avanafil in Subjects with Erectile Dysfunction. J Sex Med 2012; 9:1122-1133.

Study Design: Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 clinical trial

Description of Study: *Methods:* The 646 subjects were randomized to receive avanafil (50 mg, 100 mg, 200 mg) or placebo (1:1:1:1 ratio) throughout a 12 week treatment period. They were instructed to take the study drug 30 minutes prior to sexual activity. They were allowed to take up to two doses in a 24-hour period, provided that the doses were separated by at least 12 hours. The primary outcome of an improvement in erectile function (EF) was measured by Sexual Encounter Profile questions 2 and 3 (SEP2 and SEP3) and by the EF domain of the International Index of Erectile Function (IIEF) questionnaire. Safety endpoints included evaluation of vital signs and adverse effects at baseline and each study visit (4 weeks) during the treatment. *Results:* Mean change in percentage of successful sexual attempts (SEP2 and SEP3) and IIEF-EF domain score significantly favored all doses of avanafil over placebo. Secondary analyses showed an achievement of successful intercourse by subjects within 15 minutes of dosing. Of the sexual attempts made during this interval, 64% to 71% were successful in the avanafil groups vs 27% in the placebo group. Successful intercourse was also demonstrated > 6 hours post dosing with 59% to 83% of the avanafil groups compared to 25% in the placebo group. Within the avanafil groups, both the 100 mg and 200 mg doses showed statistical superiority over the 50 mg dose. There were no significant differences between the 100 mg and 200 mg groups. The most commonly reported adverse events in subjects taking avanafil included headache, flushing, and nasal congestion. There were no serious drug-related adverse events.

Limitations: All eight of the authors of this study had some affiliation to Vivus, which is the US manufacturer of this drug. This is also who funded this study. The conflict of interest section failed to mention Vivus's role in production of the drug and only lists the original manufacturers from Korea. It did not specify how adverse events were reported. The authors claim superiority over other studies because it included subjects with failure on previous oral ED treatment; however, the exclusion criteria lists treatment failure with previous PDE5 inhibitor use. The study also excluded patients with a history of dose-limiting adverse events to this class of drugs. This exclusion may skew the safety results in avanafil's favor. The inclusion/exclusion criteria would make extrapolation of this study's results difficult to the general patient population. The discussion attempted to make claims that were not directly evaluated in this specific study. The selectivity of the drug for PDE5 was not determined in this study and head to head analysis with other drugs from this class was not performed; therefore, they cannot speculate that avanafil is associated with fewer adverse events than these other agents.

Conclusion: Given the effective response times shown in this study, avanafil could be an effective fast-acting option in the treatment of broad spectrum ED, working as fast as 15 minutes, while not giving up the benefit of duration of activity found in other PDE5 inhibitors by remaining effective up to 6 hours. Unfortunately, this drug was not studied in patients who fail to respond to or experience dose-limiting adverse effects from other PDE5 inhibitors so it is not known whether or not it could be a valuable option in this population.

Contraindications[1,2,3,4]

Nitrates: Consistent with its known effects on the nitric oxide/cGMP pathway, avanafil may potentiate the hypotensive effects of organic nitrates and nitrites. Patients receiving nitrates in any form are not to receive avanafil. This includes any patient who receives intermittent nitrate therapies. In a life-threatening situation, nitrate therapy should only be considered if at least 12 hours has elapsed since the last dose of avanafil; medical supervision is warranted.

Hypersensitivity Reactions: Avanafil is contraindicated in patients with a known hypersensitivity to any component of the tablet. Hypersensitivity reactions have been reported, including pruritis and eyelid swelling.

Precautions[1,2,3,4]

Color Discrimination: May cause problems with patient's ability to discriminate between colors. This appears to be a dose-related impairment. Use caution in patients with retinitis pigmentosa; a minority have genetic disorders of retinal phosphodiesterases (no safety information available).

Hearing Loss: Sudden decrease or loss of hearing has been reported rarely; hearing changes may be accompanied by tinnitus and dizziness. A direct relationship between therapy and hearing loss has not been determined.

Hypotension: Drops in blood pressure may occur due to avanafil's vasodilatory properties. Use with caution in patients with left ventricular outflow obstruction (aortic stenosis or hypertrophic obstructive cardiomyopathy). These patient's may be more sensitive to hypotensive actions. Using this drug in combination with alpha-adrenergic antagonists may cause symptomatic hypotension; patients should be hemodynamically stable before starting therapy and the lowest effective dose should be used. Avoid or limit alcohol intake while taking this medication due to the increased potential risk of symptomatic hypotension.

Priapism: Has been reported (rarely) with use. Instruct patients to seek immediate medical attention if erection persists for greater than 4 hours. Use with caution in patients

who have conditions which may predispose them to priapism (sickle cell anemia, multiple myeloma, leukemia).

Vision Loss: Vision loss may occur rarely and be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). Those with a history of vision loss may be at an increased risk. Other risk factors for NAION include low cup-to-disc ratio (“crowded disc”), coronary artery disease, diabetes, hypertension, hyperlipidemia, smoking, and >50 years of age. Safety and efficacy were not studied in patients with known degenerative retinal disorders (eg, retinitis pigmentosa); use is not recommended.

Anatomical Penis Deformation: Use with caution in patients with anatomical deformation of the penis (angulation, cavernosal fibrosis, or Peyronie's disease).

Bleeding Disorders: Use with caution in patients with bleeding disorders; safety and efficacy have not been established

Cardiovascular Disease: Use is not recommended in patients with hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/100 mm Hg); unstable angina or angina during intercourse; life-threatening arrhythmias, stroke, MI, or coronary revascularization within the last 6 months; cardiac failure or coronary artery disease causing unstable angina. Safety and efficacy have not been studied in these patients. Use caution in patients with left ventricular outflow obstruction (eg, aortic stenosis). Due to the risk of cardiovascular events with sexual activity, physicians may wish to consider the cardiovascular status of their patients prior to initiating any treatment for erectile dysfunction.

Hepatic Impairment: Safety and efficacy have not been studied in patients with severe hepatic impairment (Child-Pugh class C); therefore, use in these patients is not recommended.

Peptic Ulcer Disease: Use with caution in patients with active peptic ulcer disease; safety and efficacy have not been established

Renal Impairment: Safety and efficacy have not been studied in patients with severe renal impairment or end-stage renal disease requiring dialysis, therefore, use in these patients is not recommended.

Concomitant Use of Alpha-Blockers: Use with caution in patients taking alpha-blockers due to the increased risk of hypotension. Safety of this combination may be affected by other antihypertensives and intravascular volume depletion. Patients should be hemodynamically stable prior to initiating therapy. Initiate avanafil at the lowest recommended dose.

High Potential for Interactions: Avoid use in patients taking strong CYP3A4 inhibitors (see Drug Interactions); dosage reduction recommended in patients taking moderate CYP3A4 inhibitors.

Adverse Effects[1,2,3,4]

Occurring in >10% of patients

Central nervous system

Headache (5% to 12%)

Occurring in 2%-10% of patients

Cardiovascular

Flushing (3% to 10%)

ECG abnormal (1% to 3%)

Central Nervous System

Dizziness (1% to 2%)

Neuromuscular and Skeletal

Back pain (1% to 3%)

Respiratory

Nasopharyngitis (1% to 5%)

Nasal congestion (1% to 3%)

Upper respiratory infection (1% to 3%)

Occurring in <2% of patients (Postmarketing, and/or case reports)

Abdominal discomfort
ALT increased
Angina
Arthralgia
Balanitis
Bronchitis
Color vision change
Constipation
Cough
Depression
Diarrhea
DVT
Dyspepsia
Dyspnea (exertional)
Epistaxis
Extremity pain
Fatigue
Gastritis
Gastroesophageal reflux
Hearing loss
Hematuria
Hyperglycemia

Hypertension
Hypoglycemia
Hypotension
Influenza
Insomnia
Muscle spasms
Musculoskeletal pain
Myalgia
Nausea
Nephrolithiasis
Nonarteritic ischemic optic neuropathy (NAION)
Oropharyngeal pain
Palpitations
Peripheral edema
Pollakiuria
Priapism
Pruritus
Rash
Sinusitis
Sinus congestion
Somnolence
Tinnitus
Urinary tract infection
Vertigo
Vision loss (temporary or permanent)
Vomiting
Wheezing

Drug Interactions[1,2,3,4]

Nitrates

Concomitant use of nitrates in any form is contraindicated

Alpha Blockers

If avanafil is co-administered with an alpha-blocker, patients should be stable on alpha-blocker therapy prior to initiating treatment with avanafil, and initiate avanafil therapy with 50 mg dose

Antihypertensives (Amlodipine, Enalapril)

Due to its vasodialative properties, avanafil poses a risk of potentiation of the blood pressure-lowering effects of selected antihypertensive medications. Additional reductions in blood pressure occurred following co-administration of avanafil with these agents compared with placebo

Phosphodiesterase Inhibitors (Tadalafil, Vardenafil, Sildenafil)

The safety and efficacy of avanafil administered concurrently with any other phosphodiesterase inhibitors has not been studied. Avoid use of avanafil with any other products in the same class

Alcohol

Both alcohol and avanafil act as vasodilators. Concomitant use may attenuate the blood-pressure-lowering effects of each individual compound. Substantial consumption of ethanol (e.g., greater than 3 units) in combination with avanafil may increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache

Strong CYP 3A4 Inhibitors

As a substrate of CYP 3A4, anavafil exposure may be increased by strong CYP 3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, and ritonavir. Do not use avanafil in patients taking these medications.

Moderate CYP 3A4 Inhibitors

Avanafil exposure was shown to increase when taken with moderate CYP 3A4 inhibitors such as erythromycin, amprenavir, aprepitant, diltiazem, fluconazole, fosamprenavir, and verapamil. It is not recommended to exceed 50 mg of avanafil once every 24 hours for patients taking concomitant moderate CYP3A4 inhibitors Although specific interactions have not been studied, other CYP3A4 inhibitors, including grapefruit juice, are also likely to increase avanafil exposure.

CYP 3A4 Substrates

Caution should be used when prescribing avanafil to patients receiving concomitant CYP3A4 substrates, such as amlodipine. Coadministration of avanafil with amlodipine increased the Cmax and AUC of avanafil by approximately 22% and 70%, respectively. The half-life of avanafil was prolonged to approximately 10 hrs. The Cmax and AUC of amlodipine decreased by approximately 9% and 4%, respectively. Patients should be monitored carefully and drug dosages should be adjusted based on clinical response.

Cytochrome P450 Inducers

The potential effect of CYP inducers on the pharmacokinetics of avanafil was not evaluated. The concomitant use of avanafil and CYP inducers (barbiturates, bosentan, carbamazepine, dexamethasone, phenytoin/fosphenytoin, nevirapine, rifabutin, rifampin, rifapentine, and troglitazone) is not recommended.

Desipramine

As a weak inhibitor of CYP2D6, avanafil increased the AUC and Cmax of desipramine, a CYP2D6 substrate. Although specific interactions have not been studied, other CYP2D6 substrates may be affected in a similar manner.

Omeprazole

As a weak inhibitor of CYP2C19, avanafil increased the AUC and Cmax of omeprazole, a CYP2C19 substrate. Although specific interactions have not been studied, other CYP2C19 substrates may be affected in a similar manner.

Rosiglitazone

As a weak inhibitor of CYP2C8, avanafil increased the AUC and Cmax of rosiglitazone, a CYP2C8 substrate. Although specific interactions have not been studied, other CYP2C8 substrates may be affected in a similar manner.

Dosing/Administration[1,2,3,4]

Adult Dosing

Recommended starting dose of avanafil is 100 mg orally as needed 30 minutes prior to sexual activity. Maximum frequency of use is once daily. Use the lowest effective dose. Based on clinical response, the dose may be decreased to 50 mg or increased to a maximum 200 mg

Pediatrics

Use of avanafil is not indicated in pediatric patients under the age of 18. Safety and efficacy have not been established in this population

Elderly

No dosage adjustment needed. Refer to adult dosing

Renal Impairment

Mild to Moderate ($Cl_{cr} \geq 30$ mL/minute): No dosage adjustment necessary.
Severe or Dialysis ($Cl_{cr} < 30$ mL/minute): Use is not recommended

Hepatic Impairment

Mild to Moderate (Child-Pugh class A or B): No dosage adjustment necessary
Severe (Child-Pugh class C): Use is not recommended

Use in Special Circumstances[1,2,3,4]

Pregnancy

Pregnancy Category C. Based on data from animal reproduction studies, avanafil is predicted to have a low risk for major developmental abnormalities in humans. Avanafil is not indicated for use in women. There are no adequate and well-controlled human studies of avanafil in pregnant women

Lactation

Avanafil is not indicated for use in females and is therefore not recommended during breast-feeding. It is not known if avanafil is excreted in human breast milk

Overdose [1]

Single doses up to 800 mg have been given to healthy subjects, and multiple doses up to 300 mg have been given to patients. In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance because avanafil is highly bound to plasma proteins and is not significantly eliminated in the urine

Conclusion:

Avanafil is an effective treatment option for males suffering from ED. Its main advantage over the other available PDE5 inhibitors is its faster onset of action (its onset of action is 15-30 minutes compared to about 60 minutes for the others). This allows for relatively little planning needed before the initiation of sexual activity, which is beneficial for its users. Additionally, all other agents in this class are also brand only so the aspect of cost should be comparable;

however, because availability in the US is currently unknown, the cost is yet to be determined. Its greater selectivity could decrease the incidence and severity of adverse events; however, more studies are needed to confirm this. It is known that avanafil does not cause any additional adverse events compared to the other agents in this class. That, combined with its quick onset of action, makes it a desirable therapeutic option for ED.

Recommended References:

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4. Avanafil. In: DRUGDEX® System [Internet Database]. Greenwood Village, CO: Thomson Micromedex. Updated periodically. Accessed: June 6, 2012
5. Zhao C, Kim SW, Yang DL, et al. Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. BJU International 2012.
6. Jung J, Choi S, Cho SH, et al. Tolerability and Pharmacokinetics of Avanafil, a Phosphodiesterase Type 5 Inhibitor: A Single- and Multiple-Dose, Double-Blind, Randomized, Placebo-Controlled, Dose-Escalation Study in Health Korean Male Volunteers. Clinical Therapeutics. 2010; 32(6):1178-86.
7. Goldstein I, McCullough AR, Jones LA, et al. A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Avanafil in Subjects with Erectile Dysfunction. J Sex Med 2012; 9:1122-1133.

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