CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202276Orig1s000

OFFICE DIRECTOR MEMO

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 27, 2012
TO: NDA 202276
Stendra (avanafil)
Vivus, Inc.

FROM: Victoria Kusiak, M.D., F.A.C.C.
Deputy Director, Office of Drug Evaluation III

SUBJECT: Approval Action

Stendra (avanafil) is a type 5 phosphodiesterase (PDE5) inhibitor and is highly selective for the PDE5 isoenzyme relative to other PDE5 inhibitors. It is indicated for the treatment of erectile dysfunction (ED). The physiological mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cGMP, producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Avanafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect on NO by inhibiting PDE5, which is responsible for the degradation of cGMP in the corpus cavernosum. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

This memorandum documents my concurrence with the Division of Reproductive and Urologic Products (DRUP) recommendation to approve avanafil 50 mg, 100 mg, and 200 mg for the treatment of erectile dysfunction. The recommended starting dose is 100 mg to be taken orally as needed approximately 30 minutes before sexual activity. Based upon individual efficacy and tolerability, the dose may be increased to a maximum of 200 mg or decreased to 50 mg. Recommended dosing should not exceed one exposure per 24 hours. Sexual stimulation is required for a response to treatment.

REGULATORY HISTORY

Subsequent to a pre-IND meeting held with DRUP on November 7, 2001, IND 51235 was opened for avanfil on November 30, 2001.

An End of Phase 2 (EOP2) meeting was held with the applicant on November 2, 2005 during which the applicant proposed to conduct two pivotal phase 3 trials (one in the broad ED population and one in diabetic men); one phase 3 trial in men with ED who had

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undergone radical prostatectomy; and one 12-month open label safety trial. The proposal was considered to be acceptable.

Special Protocol Assessment (SPA) evaluations were conducted by DRUP for the two pivotal phase 3 trials and for the trial to be conducted in subjects who had undergone radical prostatectomy. The proposed long term safety trial was also reviewed by DRUP prior to its initiation.

On October 20, 2010, DRUP met with the applicant for a Pre-NDA meeting. At that time, due to slower that anticipated enrollment in the trial in subjects who had undergone radical prostatectomy (Study TA-303), the Division agreed that the NDA could be submitted without the inclusion of the stalled trial, as there appeared to be adequate patient exposure in the remaining trials. Safety data from Study TA-303 were to be submitted with the 120 day Safety Update.

The NDA was submitted on June 29, 2011 and received a standard review timeframe.

CHEMISTRY MANUFACTURING and CONTROLS

There are no outstanding CMC issues. The proposed testing and acceptance criteria for both the drug substance and drug product are considered adequate to assure identity, strength, purity, and quality for all requested dosage strengths of avanafil.

CLINICAL MICROBIOLOGY

There are no clinical microbiology issues for this application.

PRECLINICAL PHARMACOLOGY/TOXICOLOGY

The toxicity profile for avanfil appears to be similar to that of other PDE5 inhibitors. The nonclinical package submitted by the applicant included general and safety pharmacology and pharmacokinetic/ADME assessments, single and repeated dose toxicology studies and a single dose phototoxicity study.

The most concerning nonclinical adverse effects were CNS toxicity and impaired fertility which occurred at low exposure multiples compared to clinical exposures.

For CNS toxicities, the no observed adverse effect level (NOAEL) in mice, dogs and rats represents exposure levels 3-5 fold higher than exposures in men at the Maximum Recommended Human Dose (MRHD) of 200 mg.

Avanafil treated rats had reduced fertility in both males and females at approximately 11 and 30 times the human exposure at a dose of 200 mg, respectively. Changes in reproductive parameters in rats included no or reduced sperm motility with increased abnormal sperm morphology including broken sperm with detached heads. The NOAEL in rats for the adverse effects on sperm were comparable to exposures in men at the

MRHD. Of note, the effects on sperm were reversible at the end of a 9 week drug free period.

Avanafil is not considered to be genotoxic and was not carcinogenic in two year rat and mouse carcinogenicity studies at systemic exposures 8-11 times higher than those observed clinically following use of 200 mg of avanafil. No teratogenic effects were observed at exposures up to 30 fold the MRHD in rats and 6 fold the MRHD in rabbits.

Based on the adverse effects reported on sperm and fertility in rats and the lack of a multiple dose study in humans, a post-marketing clinical trial will be required to further evaluate potential effects on spermatogenesis in men following repeat dose administration.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

Avanafil is rapidly absorbed after oral administration with a median Tmax of 30 to 45 minutes. The terminal elimination half life is approximately 5 hours. Avanafil is dose proportional over the recommended dose range and it is eliminated predominantly by hepatic metabolism (mainly CYP3A4). It is extensively metabolized in humans, with 62% of an oral dose excreted in the feces and 21% in the urine. Less than 0.0002% of the administered dose appeared in the semen of subjects. Avanafil is approximately 99% bound to plasma proteins and does not accumulate when administered twice daily over 7 days.

There are clinically irrelevant reductions seen in Cmax (24-39%) and AUC (1.5%) when avanafil is taken with a fatty meal.

Drug/Drug Interactions:

Avanafil is predominately metabolized by CYP3A4 and drugs that inhibit this enzyme system can increase avanafil exposure. Strong CYP3A4 inhibitors such as ketoconazole and ritonavir increased avanafil AUC and Cmax by 13 and 3 fold respectively. Moderate inhibitors such as erythromycin increased Cmax and AUC by 2 and 3 fold respectively. No *in vivo* drug-drug interaction trials were conducted with weak CYP3A4 inhibitors, nor was the potential effect of CYP inducers on the pharmacokinetics of avanafil evaluated. Avanafil is not recommended for subjects taking strong CYP3A4 inhibitors and for subjects taking moderate CYP3A4 inhibitors the recommended dose is 50 mg.

Special Populations:

Geriatric: Geriatric use has been evaluated in clinical trials with avanafil. 23% of subjects in clinical trials were age 65 years or older. No overall differences in efficacy and safety were observed in the elderly population compared to the younger population.

The AUC for avanafil was 1.2 higher in the elderly (65-80yrs) population compared to younger (19-43 yrs) men. Tmax increased by 0.19 hours from 0.56 to 0.75 hr and mean t ½ decreased by 0.9 hr from 6.5 to 5.6. These differences in the elderly are not considered to be significant.

Hepatically Impaired: In patients with mild hepatic impairment (Child-Pugh Class A), AUC and Cmax were comparable to that of healthy subjects when both were given a 200 mg dose. In patients with moderate hepatic impairment Cmax was 51% lower and AUC was 11% higher compared to healthy subjects given a 200 mg dose. No dose adjustment is considered necessary for mild to moderately hepatically impaired patients. Avanafil has not been studied in patients with severe hepatic impairment.

Renally Impaired: Mild or moderate renal impairment did not significantly impact the systemic exposure of a single 200 mg dose of avanafil. AUC decreased by 3.0% and Cmax increased by 2.8% in patients with mild renal impairment, while AUC increased by 9.1% and Cmax decreased by 2.8 % in patients with moderate renal failure. Patients with severe and end stage renal failure were not evaluated.

Pharmacodynamics:

Effects of avanafil on blood pressure (BP) were evaluated over the course of clinical trials and in directed trials. Single oral doses of 200 mg administered to healthy men resulted in mean changes in Systolic BP/Diastolic BP of -5.3/-3.7 at one hour after dosing compared to changes from baseline in the placebo group of 2.7/-0.4. The placebo adjusted reductions in BP seen with avanafil were 8.0/3.3.

As would be expected of a drug with this vasodilating mechanism of action, effects on lowering of BP were exacerbated when avanafil was administered with other vasodilators such as nitrates, alpha blockers, ACE inhibitors, and alcohol.

Of particular note is the effect on BP of combining avanafil with nitrates. In a trial designed to access the effect of the combination of avanafil and nitrates, mean sitting BP declined by 21.6/18.2 for sitting BP and by 28.0/23.5 for standing BP when nitroglycerine was administered with avanafil as opposed to a decline of 13.4/11.8 sitting and 21.1/16.5 standing with avanafil alone. 28% of avanafil treated subjects as compared to 15% of placebo treated subjects had significant decreases in BP defined as greater than or equal to a 30 mmHg decrease in systolic BP after nitroglycerin administration.

Avanafil is not expected to prolong the QT interval when taken at the recommended therapeutic dose or when taken with strong CYP3A4 inhibitors at the recommended adjusted dose. When 800 mg was given as a single dose, and at a mean Cmax 6.8 fold higher than the mean Cmax seen at the therapeutic starting dose of 100 mg, a very slight (1.6 ms) increase in QTcF was seen at one time point.

EFFICACY

The efficacy of avanafil was primarily evaluated in 2 randomized, double-blind, placebo-controlled, parallel group trials of up to 3 months duration (TA-301 and TA-302). In these 2 trials, subjects were assigned to receive avanafil 50 mg, 100 mg or 200 mg or placebo taken as needed, not to exceed 1 dose in 24 hours. Subjects were instructed to take 1 dose of trial medication approximately 30 minutes prior to initiation of sexual activity. Food and alcohol intake was not restricted.

A subset of subjects from these trials was enrolled into an open label extension trial where all eligible subjects were initially assigned to avanafil 100 mg. At any point the subjects could request to have their dose of avanafil increased to 200 mg or decreased to 50 mg based upon perceived efficacy and tolerability.

The three primary outcome measures were the erectile function domain of the International Index of Erectile Function (IIEF ED) and questions 2 and 3 from the Sexual Encounter Profile (SEP 2,3). The IIEF is a 4 week recall questionnaire that was administered at baseline and at 4 week intervals during treatment. The IIEF erectile function domain has a 30 point score where higher scores reflect better erectile function. The SEP included diary based measures of erectile function. Subjects recorded information regarding each sexual attempt made throughout the trial. The two questions on the SEP evaluated successful vaginal penetration (SEP2) and successful intercourse (SEP3).

In Study TA-301 which evaluated a general ED population, 646 men (approximately 155 per arm) with ED from various etiologies (organic, psychogenic, mixed) were evaluated. The mean age was 55.7 years (range 23-88). 85.6% of men studied were White, 13% Black, 0.9% Asian and 0.3% other races. The mean duration of ED was 6.5 years.

In this trial, avanafil at doses of 50 mg, 100 mg and 200 mg demonstrated statistically significant improvement in all 3 primary efficacy endpoints relative to placebo. For the IIEF EF Domain endpoint, the change in mean score from baseline was 2.9, 5.4, 8.3 and 9.5 for placebo, 50 mg, 100 mg and 200 mg respectively. The changes were highly statistically significant with p values (relative to placebo) of 0.0014 (50 mg), <0.0001 (100 mg), and <0.0001 (200 mg). For the endpoint referable to successful vaginal penetration (SEP2), the percent change from baseline was 7.1, 18.2, 27.2 and 29.8% for placebo, 50 mg, 100 mg, and 200 mg respectively. All changes were highly statistically significant as were the percent changes from baseline for the endpoint referable to successful intercourse (SEP3): 14.1%, 41.3%, 57.1% and 57.0% for placebo, 50 mg, 100 mg, and 200 mg respectively.

Similar highly statistically significant results were seen in Study TA-302, which evaluated the effect of avanafil on ED in 390 men with type 1 or type 2 diabetes mellitus. The mean age was 58 years (range 30-78). The population was 80.5% White, 17.2% Black, 1.5% Asian and 0.8% other races. The mean duration of ED was 6 years.

In this trial, avanafil at doses of 100 mg and 200 mg demonstrated statistically significant improvement in all three primary efficacy variables as measured by the IIEF ED domain, and the SEP2 and SEP3. Approximately 126 subjects per arm (placebo, avanafil, 100 mg, avanafil 200 mg) were studied. The change from baseline in IIEF ED was 1.8, 4.5 and 5.3 for placebo, avanafil 100 mg and avanafil 200 mg respectively. For the SEP2 endpoint the change from baseline was 7.5%, 21.5% and 25.9% for placebo, avanafil 100 mg and avanafil 200 mg respectively. For the SEP3 endpoint, the percent changes from baseline were 13.6%, 28.7% and 34.0% for placebo, avanafil 100 mg and avanafil 200 mg respectively. All changes were highly statistically significant with p values relative to placebo ranging from $p < 0.0014$ to $p < 0.0001$ for all endpoints studied.

Significant benefit of avanafil was seen in all age groups, degrees of severity of ED, and for all durations of ED. The effect of avanafil in different ethnicities could not be evaluated because there were too few non-White subjects.

SAFETY

In total, 1923 subjects were exposed to avanafil during the clinical development program: 621 in Phase 1, 360 in phase 2 and 942 in phase 3 trials. In trials where subjects used avanafil as needed, a total of 493 subjects were exposed for greater than or equal to 6 months, and 153 were treated for greater than or equal to 12 months.

In general, the overall safety profile of avanafil was similar to that of other PDE5 inhibitors. Specifically, contraindication of use with nitrates, caution to assure a cardiovascular status commensurate with permissible sexual activity, caution with use of alpha blockers, other antihypertensives, and alcohol with regard to BP, caution as to the possibility of priapism and caution with regard to vision disturbances and hearing loss are all appropriate based upon the mechanism of action (PDE5 inhibition) and/or the results of specific clinical pharmacology trials.

In three randomized, double blind, placebo controlled phase 3 trials lasting up to three months (including patients who had undergone radical prostatectomy), the mean age of the subjects was 56.4 (range 23-88 years) with 83.9% White, 13.8% Black, 1.4% Asian and < 1% Hispanic. 41.1% were current or previous smokers and 30.6% had diabetes mellitus.

The discontinuation rate due to adverse reactions in these trials was 1.4%, 2.0%, 2.0% and 1.7% for avanafil 50 mg, 100 mg, 200mg, and placebo respectively.

Adverse reactions reported by greater than or equal to 2% of subjects treated with avanafil (50 mg, 100 mg, 200 mg) were headache (5.1%, 6.9%, 10.5%), flushing (3.2%, 4.3%, 4.0%), nasal congestion (1.8%, 2.9%, 2.0%), nasopharyngitis (0.9%, 2.6%, 3.4%) and back pain (3.2%, 2.0%, 1.1%). Placebo rates for these events ranged from 0.0% to 2.9%.

In a long term open label extension trial of 712 subjects from two of the controlled trials described above, the duration of treatment was up to 12 months (493 >6 months, 153= 12 months), the mean age was 56.4 years (range 23-88 years) and the discontinuation rate due to adverse reactions was 2.8%. In this extension trial, all subjects were initially assigned to avanafil 100 mg, but could ask to have their dose increased to 200 mg or decreased to 50 mg based on their individual response to treatment. 536 subjects (75%) increased their dose to 200 mg, while 5 (<1%) decreased their dose to 50 mg.

Adverse reactions reported by greater than or equal to 2% of subjects in this open label extension included headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%) and nasal congestion (2.1%).

ADVISORY COMMITTEE

The first PDE5 inhibitor, sildenafil, was approved in 1995 for treatment of erectile dysfunction. Since then, other PDE5 inhibitor products have been approved and used in clinical practice. The safety issues associated with PDE5 inhibitor therapies are well known and can be adequately labeled. In addition, no new safety concerns were identified for avanafil. Therefore, no Advisory Committee was convened.

PEDIATRIC CONSIDERATIONS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosage regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the condition for which this product is indicated does not exist in the pediatric population, the applicant is granted a full waiver with regard to this requirement.

POSTMARKETING REQUIREMENTS and COMMITMENTS

Based upon preclinical findings in rats showing reversible changes in sperm motility and morphology and a NOAEL near the MRHD, a multi-dose clinical trial evaluating the effects of avanafil on sperm motility in humans will be required post-approval. The single dose sperm study conducted in humans submitted by the applicant with the NDA showing no effects on human sperm was determined to be inadequate as a basis for assessment of the potential for avanafil to potentially affect fertility because the conclusion was based upon a single dose trial. A subsequent clinical trial to further evaluate the potential effects of avanafil on spermatogenesis in men following repeat dose administration will be required. Until such time as the multiple-dose clinical trial is completed and reviewed, the labeling will indicate that the effect of avanafil on human spermatogenesis is unknown.

Although there were few reports of vision related adverse reactions in the overall safety database, given the experience with other PDE5 inhibitors used for this indication, information on the potential effect of avanafil on vision related parameters is also required. The specific vision related investigations conducted as parts of studies HP-01 and TA-016 are not considered adequate to address this requirement, because in HP-01(16 subjects) and in TA-016 (24 subjects), only color vision was assessed, as opposed to full vision parameters. Therefore, there will be a post-marketing requirement for a single dose clinical trial in humans to evaluate multiple measures of vision performance including visual acuity, intraocular pressure, pupillometry and formal color vision testing in the same study, on the same subjects.

Labeling

The final label was reviewed by SEALD. It was agreed upon and received from the applicant on April 26, 2012.

TRADENAME REVIEW

The applicant previously submitted three proprietary names for review that were rejected. The proposed names of (b) (4) (July 21, 2011), (b) (4) (November 1, 2011) and (b) (4) (March 5, 2012) were rejected for safety reasons.

On April 24, 2012, the proprietary name of Stendra was accepted by FDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VICTORIA KUSIAK
04/27/2012