

Center for Drug Evaluation and Research

Viagra (Sildenafil)

“Joint Clinical Review” for NDA-20-895

Section 9, page 57 through Section 10.7, page 70

Pages 57-68

Deleted

as Draft Labeling

exemption (b)(4)

10. Summary and recommendations

10.1. Chemistry

The only outstanding issue pertains to assignment of an expiration date of 12 or 24 months.

10.2. Pharmacology and toxicology

There are no outstanding issues or concerns.

10.3. Biopharmaceutics

There are somewhat conflicting data concerning the effect of CYP 3A4 inhibitors on the pharmacokinetics of sildenafil. Recommended labeling reflects the larger observed effect. The sponsor might reasonably elect to attempt to resolve the discrepancy with additional data.

The adequacy of proposed methods for dissolution testing cannot be evaluated until the sponsor provides dissolution profiles for all proposed tablet strengths using the proposed methods.

The sponsor should be requested to provide dissolution data comparing formulations S00406AC and S00394AD, used in key clinical studies, to the formulation proposed for marketing.

10.4. Effectiveness

Sildenafil 25 to 100 mg was associated with dose-related improvements in erectile function and sexual performance in subjects with erectile dysfunction of various (often ill-characterized) etiologies, including subjects with mild to fairly severe impairment. Improvement in sexual performance was assessed in placebo-controlled studies utilizing a retrospective questionnaire, and it was confirmed using subject diaries.

The studies are sufficient to indicate the drug for use in patients with 'organic' etiologies, including diabetes and spinal cord injury, and in patients with psychogenic erectile dysfunction. Diabetics generally showed a smaller benefit than did other groups.

The primary effect of sildenafil is to *enable* an erection sufficient for sexual intercourse, in the setting of appropriate sexual stimulation. In this respect, it differs from intracavernosal or transurethral alprostadil which *produce* an erection. It seems likely, then, that these other treatments may be effective in some patients for whom sildenafil is ineffective, but this has not been addressed in any trial.

In studies where dose-titration was permitted, most subjects ended study on the highest available dose (usually 100 mg).

The time course of sildenafil's effects has not been well-characterized, but it probably corresponds roughly with the time course of plasma levels of sildenafil and its active metabolite, UK-103,320—0.5 to several hours after dosing.

10.5. Safety

There were 9 cardiovascular deaths among subjects receiving sildenafil, versus one non-cardiovascular death on placebo. Only 2 of the deaths on sildenafil occurred in subjects without substantial risk factors. In no case was sildenafil considered—by the investigator, the sponsor, or the clinical reviewers—to have played a likely role.

Withdrawals for adverse events were no more common on sildenafil than on placebo. Overall, withdrawals from placebo were substantially higher, largely attributable to differences in withdrawal for lack of effectiveness.

Many common treatment-related adverse events—notably headache, vasodilation, dyspepsia, and vision disturbance—were clearly dose-related. At least small clinical studies explored doses up to 800 mg. Doses above the recommended maximum (100 mg) produced higher incidences of events seen at lower doses, but no new phenomena. These adverse events were dose-limiting, but they were rarely serious.

Sildenafil produces a peak reduction in blood pressure of about 8/6 mmHg accompanied by an increase in heart rate, around the time of the peak plasma concentration. Co-administration of a nitric oxide donor results in a substantially larger effect on blood pressure and heart rate.

Effects of sildenafil on vision appear to be restricted to aberrations in color discrimination which are ascertainable by careful testing much more often than they result in subjective complaints. Available evidence suggests that effects of sildenafil on vision do not represent a safety hazard.

10.6. Recommendation

Sildenafil should be approved for the treatment of erectile dysfunction.

10.7. Comments on label

Section 9 of this review contains the clinical reviewers' recommendations for the sponsor's label.

The reviewers removed the quantitative description of the results from the sexual function questionnaire because it would not communicate anything useful to the prescribing physician.

The reviewers added a statement concerning sexual performance to the indication for use, comparable to the statement in the MUSE label.

The reviewers concurred with the sponsor's plan to list common adverse events from the titration studies, since that trial design probably better reflects clinical practice.