

Generic Name: Sildenafil citrate
Trade Name: VIAGRA®
CDS Effective Date: July 02, 2018
Supersedes: August 31, 2015

CIMETIDINE (800 MG), A NONSPECIFIC CYP INHIBITOR, CAUSED A 56% INCREASE IN PLASMA SILDENAFIL CONCENTRATIONS WHEN CO-ADMINISTERED WITH VIAGRA (50 MG) TO HEALTHY VOLUNTEERS.

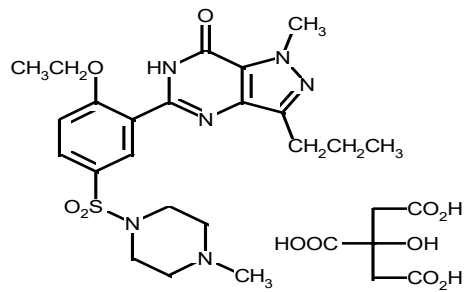
WHEN A SINGLE 100 MG DOSE OF VIAGRA WAS ADMINISTERED WITH ERYTHROMYCIN, A MODERATE CYP3A4 INHIBITOR, AT STEADY STATE (500 MG BID FOR 5 DAYS), THERE WAS A 182% INCREASE IN SILDENAFIL SYSTEMIC EXPOSURE (AUC). IN ADDITION, IN A STUDY PERFORMED IN HEALTHY MALE VOLUNTEERS, CO-ADMINISTRATION OF THE HIV PROTEASE INHIBITOR SAQUINAVIR, ALSO A CYP3A4 INHIBITOR, AT STEADY STATE (1200 MG TID) WITH VIAGRA (100 MG SINGLE DOSE) RESULTED IN A 140% INCREASE IN SILDENAFIL C_{MAX} AND A 210% INCREASE IN SILDENAFIL AUC. VIAGRA HAD NO EFFECT ON SAQUINAVIR PHARMACOKINETICS. STRONGER CYP3A4 INHIBITORS SUCH AS KETOCONAZOLE OR ITRACONAZOLE WOULD BE EXPECTED TO HAVE STILL GREATER EFFECTS, AND POPULATION DATA FROM PATIENTS IN CLINICAL TRIALS DID INDICATE A REDUCTION IN SILDENAFIL CLEARANCE WHEN IT WAS CO-ADMINISTERED WITH CYP3A4 INHIBITORS (SUCH AS KETOCONAZOLE, ERYTHROMYCIN, OR CIMETIDINE) (SEE DOSAGE AND ADMINISTRATION).

IN ANOTHER STUDY IN HEALTHY MALE VOLUNTEERS, CO-ADMINISTRATION WITH THE HIV PROTEASE INHIBITOR RITONAVIR, WHICH IS A HIGHLY POTENT P450 INHIBITOR, AT STEADY STATE (500 MG BID) WITH VIAGRA (100 MG SINGLE DOSE) RESULTED IN A 300% (4-FOLD) INCREASE IN SILDENAFIL C_{MAX} AND A 1000% (11-FOLD) INCREASE IN SILDENAFIL PLASMA AUC. AT 24 HOURS THE PLASMA LEVELS OF SILDENAFIL WERE STILL APPROXIMATELY 200 NG/ML, COMPARED TO APPROXIMATELY 5 NG/ML WHEN SILDENAFIL WAS DOSED ALONE. THIS IS CONSISTENT WITH RITONAVIR'S MARKED EFFECTS ON A BROAD RANGE OF P450 SUBSTRATES. VIAGRA HAD NO EFFECT ON RITONAVIR PHARMACOKINETICS (SEE DOSAGE AND ADMINISTRATION).

DESCRIPTION

VIAGRA®, an oral therapy for erectile dysfunction, is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP) -specific phosphodiesterase type 5 (PDE5).

Sildenafil citrate is designated chemically as 1-[[3-(6, 7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4, 3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:



Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water and a molecular weight of 666.7. VIAGRA (sildenafil citrate) is formulated as blue, film-coated rounded-diamond-shaped tablets equivalent to 25 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methyl cellulose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.

CLINICAL PHARMACOLOGY

Mechanism of Action

The physiologic 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 cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

Studies *in vitro* have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, >80-fold for PDE1, >700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10 and PDE11). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina which is involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels (see **Pharmacodynamics**).

In addition to human corpus cavernosum smooth muscle, PDE5 is also found in lower concentrations in other tissues including platelets, vascular and visceral smooth muscle, and skeletal muscle. The inhibition of PDE5 in these tissues by sildenafil may be the basis

for the enhanced platelet antiaggregatory activity of nitric oxide observed *in vitro*, an inhibition of platelet thrombus formation *in vivo* and peripheral arterial-venous dilatation *in vivo*.

Pharmacokinetics and Metabolism

VIAGRA is rapidly absorbed after oral administration, with mean absolute bioavailability of about 41%. Its pharmacokinetics are dose-proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly cytochrome P450 3A4) and is converted to an active metabolite with properties similar to the parent, sildenafil. The concomitant use of potent cytochrome P450 3A4 inhibitors (e.g., erythromycin, ketoconazole, itraconazole) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil (see **DOSAGE AND ADMINISTRATION**). Both sildenafil and the metabolite have terminal half-lives of about 4 hours.

Mean sildenafil plasma concentrations measured after the administration of a single oral dose of 100 mg to healthy male volunteers is depicted below:

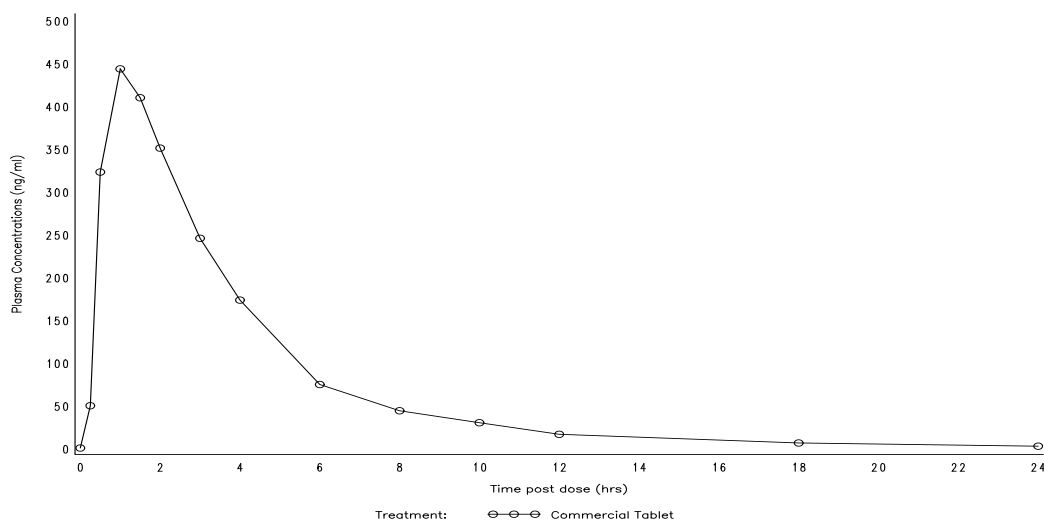


Figure 1: Mean Sildenafil Plasma Concentrations in Healthy Male Volunteers.

Absorption and Distribution: VIAGRA is rapidly absorbed. Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When VIAGRA is taken with a high fat meal, the rate of absorption is reduced, with a mean delay in T_{max} of 60 minutes and a mean reduction in C_{max} of 29%, however, the extent of absorption was not significantly affected (AUC decreased by 11%). The mean steady-state volume of distribution (V_{ss}) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Based upon measurements of sildenafil in semen of healthy volunteers 90 minutes after dosing, less than 0.001% of the administered dose may appear in the semen of patients.

Metabolism and Excretion: Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is itself further metabolized. This metabolite has a PDE selectivity profile similar to sildenafil and an *in vitro* potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.

The total body clearance of sildenafil is 41 L/h with a resultant terminal phase half-life of 3-5 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). Similar values for pharmacokinetic parameters were seen in normal volunteers and in the patient population, using a population pharmacokinetic approach.

Pharmacokinetics in Special Populations

Elderly: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, resulting in approximately 90% higher plasma concentrations of sildenafil and the active N-desmethyl metabolite compared to those seen in healthy younger volunteers (18-45 years). Due to age-differences in plasma protein binding, the corresponding increase in free sildenafil plasma concentration was approximately 40%.

Renal Insufficiency: In volunteers with mild ($CL_{cr}=50-80$ mL/min) and moderate ($CL_{cr}=30-49$ mL/min) renal impairment, the pharmacokinetics of a single oral dose of sildenafil (50 mg) were not altered. In volunteers with severe ($CL_{cr}\leq 30$ mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and C_{max} compared to age-matched volunteers with no renal impairment.

In addition, N-desmethyl metabolite AUC and C_{max} values were significantly increased 200% and 79% respectively in subjects with severe renal impairment compared to subjects with normal renal function.

Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh class A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and C_{max} (47%) compared to age-matched volunteers with no hepatic impairment. The pharmacokinetics of sildenafil in patients with severely impaired hepatic function (Child-Pugh class C) have not been studied.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Effects of VIAGRA on Erectile Response: In eight double-blind, placebo-controlled crossover studies of patients with either organic or psychogenic erectile dysfunction, sexual stimulation resulted in improved erections, as assessed by an objective measurement of hardness and duration of erections (RigiScan[®]), after VIAGRA administration compared with placebo. Most studies assessed the efficacy of VIAGRA approximately 60 minutes post-dose. The erectile response, as assessed by RigiScan[®], generally increased with increasing sildenafil dose and plasma concentration. The time course of effect was examined in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours.

Effects of VIAGRA on Blood Pressure: Single oral doses of sildenafil (100 mg) administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8.3/5.3 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different than placebo at 8 hours. Similar effects on blood pressure were noted with 50 mg and 100 mg of VIAGRA, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates (see **CONTRAINDICATIONS**).

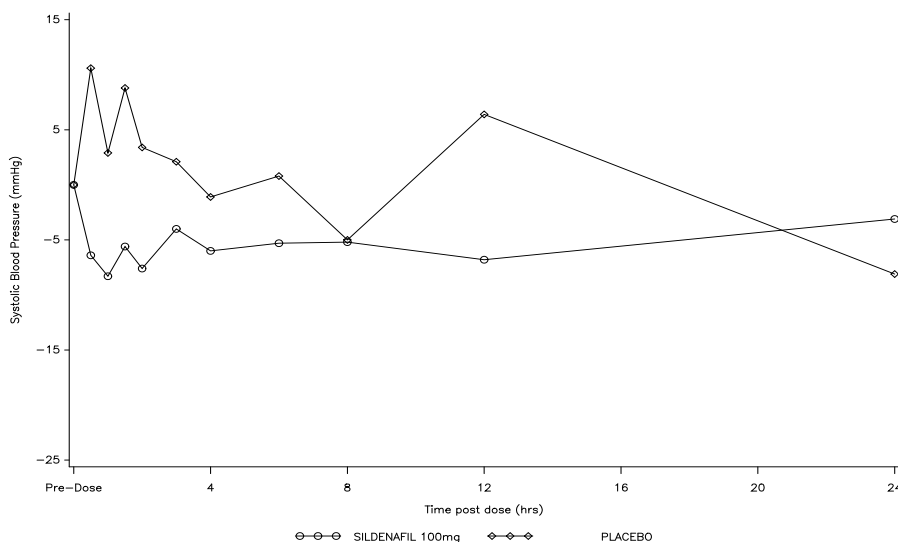


Figure 2: Mean Change from Baseline in Sitting Systolic Blood Pressure, Healthy Volunteers.

Effects of VIAGRA on Cardiac Parameters: Single oral doses of sildenafil up to 100 mg produced no clinically relevant changes in the ECGs of normal male volunteers.

Studies have produced relevant data on the effects of VIAGRA on cardiac output. In one small, open-label, uncontrolled, pilot study, eight patients with stable ischemic heart disease underwent Swan-Ganz catheterization. A total dose of 40 mg sildenafil was administered by four intravenous infusions.

The results from this pilot study are shown in Table 1; the mean resting systolic and diastolic blood pressures decreased by 7% and 10% compared to baseline in these patients. Mean resting values for right atrial pressure, pulmonary artery pressure, pulmonary artery occluded pressure and cardiac output decreased by 28%, 28%, 20% and 7% respectively. Even though this total dosage produced plasma sildenafil concentrations which were approximately 2 to 5 times higher than the mean maximum plasma concentrations following a single oral dose of 100 mg in healthy male volunteers, the hemodynamic response to exercise was preserved in these patients.

TABLE 1. HEMODYNAMIC DATA IN PATIENTS WITH STABLE ISCHEMIC HEART DISEASE AFTER IV ADMINISTRATION OF 40 MG SILDENAFIL

Means ± SD	At rest				After 4 minutes of exercise			
	n	Baseline (B2)	n	Sildenafil (D1)	n	Baseline	n	Sildenafil
PAOP (mmHg)	8	8.1 ± 5.1	8	6.5 ± 4.3	8	36.0 ± 13.7	8	27.8 ± 15.3
Mean PAP (mmHg)	8	16.7 ± 4	8	12.1 ± 3.9	8	39.4 ± 12.9	8	31.7 ± 13.2
Mean RAP (mmHg)	7	5.7 ± 3.7	8	4.1 ± 3.7	-	-	-	-
Systolic SAP (mmHg)	8	150.4 ± 12.4	8	140.6 ± 16.5	8	199.5 ± 37.4	8	187.8 ± 30.0
Diastolic SAP (mmHg)	8	73.6 ± 7.8	8	65.9 ± 10	8	84.6 ± 9.7	8	79.5 ± 9.4
Cardiac output (L/min)	8	5.6 ± 0.9	8	5.2 ± 1.1	8	11.5 ± 2.4	8	10.2 ± 3.5
Heart rate (bpm)	8	67 ± 11.1	8	66.9 ± 12	8	101.9 ± 11.6	8	99.0 ± 20.4

In a double blind study, 144 patients with erectile dysfunction and chronic stable angina limited by exercise, not receiving chronic oral nitrates, were randomized to a single dose of placebo or VIAGRA 100 mg 1 hour prior to exercise testing. The primary endpoint was time to limiting angina in the evaluable cohort. The mean times (adjusted for baseline) to onset of limiting angina were 423.6 and 403.7 seconds for sildenafil (N=70) and placebo, respectively. These results demonstrated that the effect of VIAGRA on the primary endpoint was statistically non-inferior to placebo.

A randomized, double-blind, placebo-controlled, flexible-dose study (sildenafil up to 100 mg) in males (N=568) with erectile dysfunction and arterial hypertension taking two or more antihypertensive agents was conducted. Sildenafil improved the erections in 71% of men compared to 18% in the placebo group, and 62% of attempts at sexual intercourse were successful with sildenafil compared to 26% on placebo. The incidence of adverse events was consistent with observations in other patient populations, as well as in the subjects taking three or more antihypertensive agents.

Effects of VIAGRA on Vision: At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the

Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to twice the maximum recommended dose revealed no effects of VIAGRA on visual acuity, intraocular pressure, or pupillometry.

Clinical Studies

In clinical studies, VIAGRA was assessed for its effect on the ability of men with erectile dysfunction (ED) to engage in sexual activity and in many cases specifically on the ability to achieve and maintain an erection sufficient for satisfactory sexual activity. VIAGRA was evaluated primarily in 21 randomized, double-blind, placebo-controlled trials of up to 6 months in duration, using a variety of study designs (fixed dose, titration, parallel, crossover). VIAGRA was administered to more than 3,000 patients aged 19 to 87 years, with ED of various etiologies (organic, psychogenic, mixed) with a mean duration of 5 years. VIAGRA demonstrated statistically significant improvement compared to placebo in all 21 studies. The studies that established benefit demonstrated improvements in success rates for sexual intercourse compared with placebo.

The effectiveness of VIAGRA was evaluated in most studies using several assessment instruments. The primary measure in the principal studies was a sexual function questionnaire (the International Index of Erectile Function - IIEF) administered during a 4-week treatment-free run-in period, at baseline, at follow-up visits, and at the end of double-blind, placebo-controlled, at-home treatment. Two of the questions from the IIEF served as primary study endpoints; categorical responses were elicited to questions about (1) the ability to achieve erections sufficient for sexual intercourse and (2) the maintenance of erections after penetration. The patient addressed both questions at the final visit for the last 4 weeks of the study. The possible categorical responses to these questions were (0) no attempted intercourse, (1) never or almost never, (2) a few times, (3) sometimes, (4) most times, and (5) almost always or always. Also collected as part of the IIEF was information about other aspects of sexual function, including information on erectile function, orgasm, desire, satisfaction with intercourse, and overall sexual satisfaction. Sexual function data were also recorded by patients in a daily diary. In addition, patients were asked a global efficacy question and an optional partner questionnaire was administered.

The effect on one of the major end points, maintenance of erections after penetration, is shown in Figure 3, for the pooled results of 5 fixed-dose, dose-response studies of greater than one month duration, showing response according to baseline function. Results with all doses have been pooled, but scores showed greater improvement at the 50 and 100 mg doses than at 25 mg. The pattern of responses was similar for the other principal question, the ability to achieve an erection sufficient for intercourse. The titration studies, in which most patients received 100 mg, showed similar results. Figure 3 shows that regardless of the baseline levels of function, subsequent function in patients treated with VIAGRA was better than that seen in patients treated with placebo. At the same time, on-treatment function was better in treated patients who were less impaired at baseline.

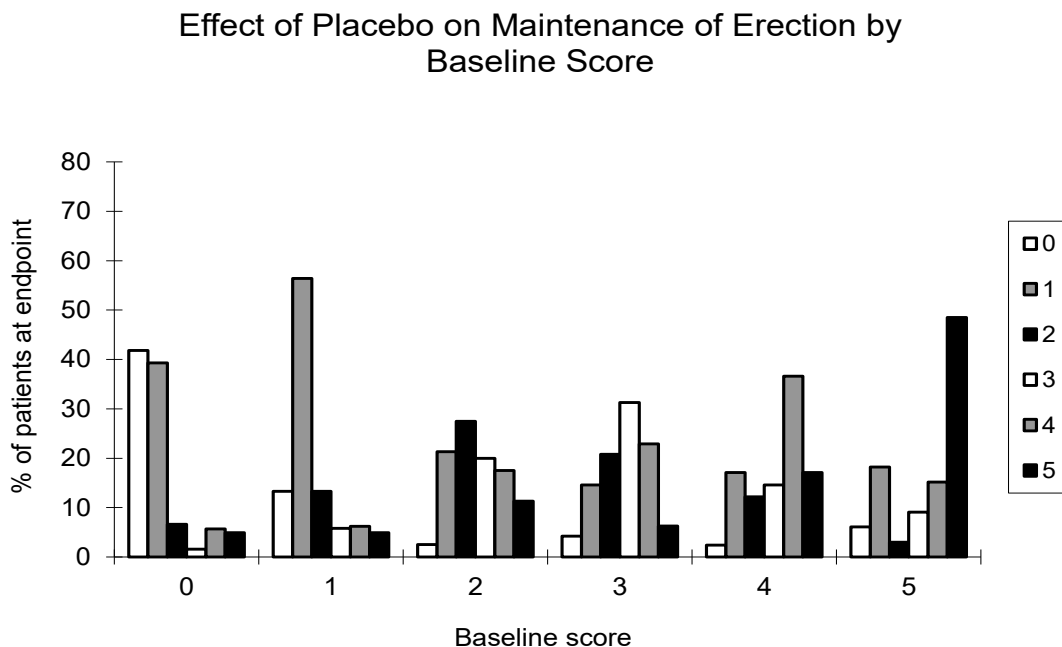
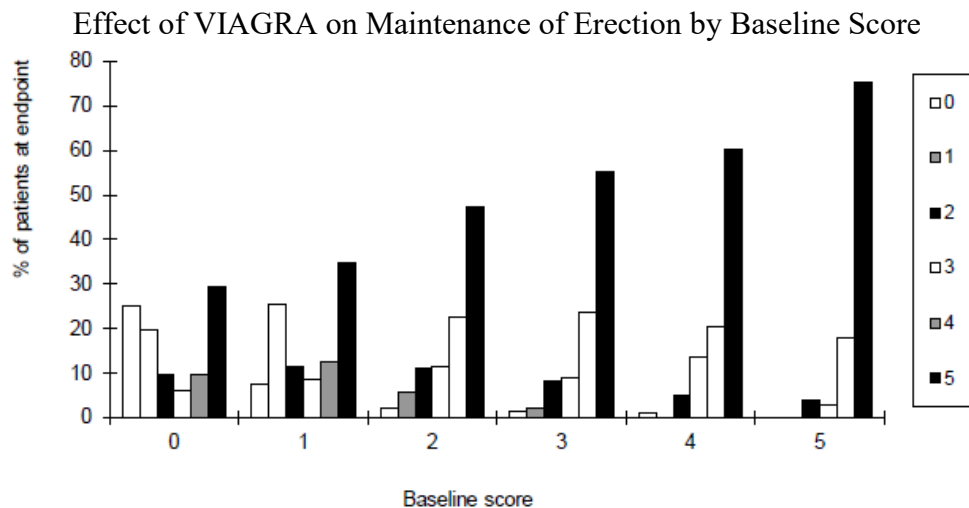
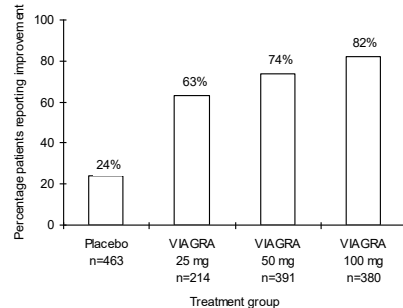


Figure 3. Effect of VIAGRA and Placebo on Maintenance of Erection by Baseline Score.

The frequency of patients reporting improvement of erections in response to a global question in four of the randomized, double-blind, parallel, placebo-controlled fixed dose studies (1797 patients) of 12 to 24 weeks duration is shown in Figure 4. These patients had erectile dysfunction at baseline that was characterized by median categorical scores of 2 (a few times) on principal IIEF questions. Erectile dysfunction was attributed to organic (58%; generally not characterized, but including diabetes and excluding spinal cord injury), psychogenic (17%), or mixed (24%) etiologies. 63%, 74%, and 82% of the patients on

25 mg, 50 mg and 100 mg of VIAGRA, respectively, reported an improvement in their erections, compared to 24% on placebo. In the titration studies (n=644) (with most patients eventually receiving 100 mg), results were similar.



Overall treatment $p < 0.0001$

Figure 4. Percentage of Patients Reporting an Improvement in Erections.

The patients in studies had varying degrees of ED. One-third to one-half of the subjects in these studies reported successful intercourse at least once during a 4-week, treatment-free run-in period.

In many of the studies, of both fixed dose and titration designs, daily diaries were kept by patients. In these studies, involving about 1600 patients, analyses of patient diaries showed no effect of VIAGRA on rates of attempted intercourse (about 2 per week), but there was clear treatment-related improvement in sexual function: per patient weekly success rates averaged 1.3 on 50-100 mg of VIAGRA vs. 0.4 on placebo; similarly, group mean success rates (total successes divided by total attempts) were about 66% on VIAGRA vs. about 20% on placebo.

During 3 to 6 months of double-blind treatment or longer-term (1 year), open-label studies, few patients withdrew from active treatment for any reason, including lack of effectiveness. At the end of the long-term study, 88% of patients reported that VIAGRA improved their erections.

Men with untreated ED had relatively low baseline scores for all aspects of sexual function measured (again using a 5-point scale) in the IIEF. VIAGRA improved these aspects of sexual function: frequency, firmness and maintenance of erections; frequency of orgasm; frequency and level of desire; frequency, satisfaction and enjoyment of intercourse; and overall relationship satisfaction.

One randomized, double-blind, flexible-dose, placebo-controlled study included only patients with erectile dysfunction attributed to complications of diabetes mellitus (n=268). As in the other titration studies, patients were started on 50 mg and allowed to adjust the dose up to 100 mg or down to 25 mg of VIAGRA; all patients, however, were receiving 50 mg or 100 mg at the end of the study. There were highly statistically significant improvements on the two principal IIEF questions (frequency of successful penetration

during sexual activity and maintenance of erections after penetration) on VIAGRA compared to placebo. On a global improvement question, 57% of VIAGRA patients reported improved erections versus 10% on placebo. Diary data indicated that on VIAGRA, 48% of intercourse attempts were successful versus 12% on placebo.

One randomized, double-blind, placebo-controlled, crossover, flexible-dose (up to 100 mg) study of patients with erectile dysfunction resulting from spinal cord injury (n=178) was conducted. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA. On a global improvement question, 83% of patients reported improved erections on VIAGRA versus 12% on placebo. Diary data indicated that on VIAGRA, 59% of attempts at sexual intercourse were successful compared to 13% on placebo.

Across all trials, VIAGRA improved the erections of 43% of radical prostatectomy patients compared to 15% on placebo.

Subgroup analyses of responses to a global improvement question in patients with psychogenic etiology in two fixed-dose studies (total n=179) and two titration studies (total n=149) showed 84% of VIAGRA patients reported improvement in erections compared with 26% of placebo. The changes from baseline in scoring on the two end point questions (frequency of successful penetration during sexual activity and maintenance of erections after penetration) were highly statistically significantly in favor of VIAGRA. Diary data in two of the studies (n=178) showed rates of successful intercourse per attempt of 70% for VIAGRA and 29% for placebo.

A review of population subgroups demonstrated efficacy regardless of baseline severity, etiology, race and age. VIAGRA was effective in a broad range of ED patients, including those with a history of coronary artery disease, hypertension, other cardiac disease, peripheral vascular disease, diabetes mellitus, depression, coronary artery bypass graft (CABG), radical prostatectomy, transurethral resection of the prostate (TURP) and spinal cord injury, and in patients taking antidepressants/antipsychotics and antihypertensives/diuretics.

Analysis of the safety database showed no apparent difference in the side effect profile in patients taking VIAGRA with and without antihypertensive medication. This analysis was performed retrospectively, and was not powered to detect any pre-specified difference in adverse reactions.

INDICATION AND USAGE

VIAGRA is indicated for the treatment of erectile dysfunction.

CONTRAINDICATIONS

Consistent with its known effects on the nitric oxide/cGMP pathway (see **CLINICAL PHARMACOLOGY**), VIAGRA was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

After patients have taken VIAGRA, it is unknown when nitrates, if necessary, can be safely administered. Based on the pharmacokinetic profile of a single 100 mg oral dose given to healthy normal volunteers, the plasma levels of sildenafil at 24 hours post-dose are approximately 2 ng/mL (compared to peak plasma levels of approximately 440 ng/mL) (see **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**). **IN THE FOLLOWING PATIENTS: AGE >65, HEPATIC IMPAIRMENT (E.G., CIRRHOSIS), SEVERE RENAL IMPAIRMENT (E.G., CREATININE CLEARANCE <30 ML/MIN), AND CONCOMITANT USE OF POTENT CYTOCHROME P450 3A4 INHIBITORS (ERYTHROMYCIN), PLASMA LEVELS OF SILDENAFIL AT 24 HOURS POST-DOSE HAVE BEEN FOUND TO BE 3 TO 8 TIMES HIGHER THAN THOSE SEEN IN HEALTHY VOLUNTEERS.** Although plasma levels of sildenafil at 24 hours post-dose are much lower than at peak concentration, it is unknown whether nitrates can be safely co-administered at this time point.

VIAGRA is contraindicated in patients with a known hypersensitivity to any component of the tablet.

The co-administration of PDE5 inhibitors, including sildenafil, with guanylate cyclase stimulators, such as riociguat, is contraindicated as it may potentially lead to symptomatic hypotension.

WARNINGS

There is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease. Therefore, treatments for erectile dysfunction, including VIAGRA, should not be generally used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status.

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage and transient ischemic attack have been reported post-marketing in temporal association with the use of sildenafil for erectile dysfunction. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a

few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors.

In clinical trials, sildenafil has been shown to have systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.3/5.3 mmHg) (see **CLINICAL PHARMACOLOGY: Pharmacodynamics**). While this normally would be expected to be of little consequence in most patients, prior to prescribing VIAGRA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects, especially in combination with sexual activity.

Non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision or loss of vision, has been reported rarely post-marketing with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors such as low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. An observational study evaluated whether recent use of PDE5 inhibitors, as a class, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged ≥ 50 per year in the general population. In case of sudden visual loss, patients should be advised to stop taking sildenafil and consult a physician immediately.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore physicians should discuss this risk with these patients and whether they could be adversely affected by use of PDE5 inhibitors. PDE5 inhibitors, including sildenafil, should be used with caution in these patients and only when the anticipated benefits outweigh the risks.

Patients with the following underlying conditions can be particularly sensitive to the actions of vasodilators including VIAGRA – those with left ventricular outflow obstruction (e.g., aortic stenosis, idiopathic hypertrophic subaortic stenosis) and those with severity impaired autonomic control of blood pressure.

There is no controlled clinical data on the safety or efficacy of VIAGRA in the following groups; if prescribed, this should be done with caution.

- Patients who have suffered a myocardial infarction, stroke, or life-threatening arrhythmia within the last 6 months;
- Patients with resting hypotension (BP <90/50) or hypertension (BP >170/110);
- Patients with cardiac failure or coronary artery disease causing unstable angina;
- Patients with retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases).

Prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

THE CONCOMITANT ADMINISTRATION OF THE PROTEASE INHIBITOR RITONAVIR SUBSTANTIALLY INCREASES SERUM CONCENTRATIONS OF SILDENAFIL (11-FOLD INCREASE IN AUC). IF VIAGRA IS PRESCRIBED TO PATIENTS TAKING RITONAVIR, CAUTION SHOULD BE USED. DATA FROM SUBJECTS EXPOSED TO HIGH SYSTEMIC LEVELS OF SILDENAFIL ARE LIMITED. VISUAL DISTURBANCES OCCURRED MORE COMMONLY AT HIGHER LEVELS OF SILDENAFIL EXPOSURE. DECREASED BLOOD PRESSURE, SYNCOPE, AND PROLONGED ERECTION WERE REPORTED IN SOME HEALTHY VOLUNTEERS EXPOSED TO HIGH DOSES OF SILDENAFIL (200-800 MG). TO DECREASE THE CHANCE OF ADVERSE EVENTS IN PATIENTS TAKING RITONAVIR, A DECREASE IN SILDENAFIL DOSAGE IS RECOMMENDED (SEE DRUG INTERACTIONS, ADVERSE REACTIONS AND DOSAGE AND ADMINISTRATION).

PRECAUTIONS

General

The evaluation of erectile dysfunction should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Before prescribing VIAGRA, it is important to note the following:

Patients on multiple antihypertensive medications were included in the pivotal clinical trials for VIAGRA. In a separate drug interaction study, when amlodipine, 5 mg or 10 mg, and VIAGRA, 100 mg were orally administered concomitantly to hypertensive patients mean additional blood pressure reduction of 8 mmHg systolic and 7 mmHg diastolic were noted (see **Drug Interactions**).

When the alpha blocker doxazosin (4 mg) and VIAGRA (25 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH), mean additional reductions of supine blood pressure of 7 mmHg systolic were observed. When higher doses of VIAGRA and doxazosin (4 mg) were administered simultaneously, there were infrequent reports of patients who experienced symptomatic postural hypotension within 1 to 4 hours of dosing. Simultaneous administration of VIAGRA to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients. Therefore,

VIAGRA doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker. In addition, physicians should advise patients what to do in the event of postural hypotensive symptoms.

The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration.

VIAGRA should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia).

The safety and efficacy of combinations of VIAGRA with other PDE5 inhibitors, or other treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

Sudden decrease or loss of hearing has been reported in a small number of post-marketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. In case of sudden decrease or loss of hearing patients should be advised to stop taking sildenafil and consult a physician promptly.

In humans, VIAGRA has no effect on bleeding time when taken alone or with acetyl salicylic acid. *In vitro* studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside (a nitric oxide donor). The combination of heparin and VIAGRA had an additive effect on bleeding time in the anesthetized rabbit, but this interaction has not been studied in humans.

Information for Patients

Physicians should discuss with patients the contraindication of VIAGRA with regular and/or intermittent use of organic nitrates.

Physicians should discuss with patients the potential cardiac risk of sexual activity in patients with preexisting cardiovascular risk factors. Patients who experience symptoms (e.g., angina pectoris, dizziness, nausea) upon initiation of sexual activity should be advised to refrain from further activity and should discuss the episode with their physician.

Physicians should warn patients that prolonged erections greater than 4 hours and priapism (painful erections greater than 6 hours in duration) have been reported infrequently since market approval of VIAGRA. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency may result.

Physicians should advise patients that simultaneous administration of VIAGRA doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Therefore, VIAGRA doses above 25 mg should not be taken within four hours of taking an alpha-blocker.

The use of VIAGRA offers no protection against sexually transmitted diseases. Counseling of patients about the protective measures necessary to guard against sexually transmitted diseases, including the Human Immunodeficiency Virus (HIV), may be considered.

Drug Interactions

Effects of Other Drugs on VIAGRA

***In vitro* studies:** Sildenafil metabolism is principally mediated by the cytochrome P450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance and inducers of these isoenzymes may increase sildenafil clearance.

***In vivo* studies:**

CIMETIDINE (800 MG), A NONSPECIFIC CYP INHIBITOR, CAUSED A 56% INCREASE IN PLASMA SILDENAFIL CONCENTRATIONS WHEN CO-ADMINISTERED WITH VIAGRA (50 MG) TO HEALTHY VOLUNTEERS.

WHEN A SINGLE 100 MG DOSE OF VIAGRA WAS ADMINISTERED WITH ERYTHROMYCIN, A MODERATE CYP3A4 INHIBITOR, AT STEADY STATE (500 MG BID FOR 5 DAYS), THERE WAS A 182% INCREASE IN SILDENAFIL SYSTEMIC EXPOSURE (AUC). IN ADDITION, IN A STUDY PERFORMED IN HEALTHY MALE VOLUNTEERS, COADMINISTRATION OF THE HIV PROTEASE INHIBITOR SAQUINAVIR, ALSO A CYP3A4 INHIBITOR, AT STEADY STATE (1200 MG TID) WITH VIAGRA (100 MG SINGLE DOSE) RESULTED IN A 140% INCREASE IN SILDENAFIL C_{MAX} AND A 210% INCREASE IN SILDENAFIL AUC. VIAGRA HAD NO EFFECT ON SAQUINAVIR PHARMACOKINETICS. STRONGER CYP3A4 INHIBITORS SUCH AS KETOCONAZOLE OR ITRACONAZOLE WOULD BE EXPECTED TO HAVE STILL GREATER EFFECTS, AND POPULATION DATA FROM PATIENTS IN CLINICAL TRIALS DID INDICATE A REDUCTION IN SILDENAFIL CLEARANCE WHEN IT WAS CO-ADMINISTERED WITH CYP3A4 INHIBITORS (SUCH AS KETOCONAZOLE, ERYTHROMYCIN, OR CIMETIDINE) (SEE DOSAGE AND ADMINISTRATION).

IN ANOTHER STUDY IN HEALTHY MALE VOLUNTEERS, CO-ADMINISTRATION WITH THE HIV PROTEASE INHIBITOR RITONAVIR, WHICH IS A HIGHLY POTENT P450 INHIBITOR, AT STEADY STATE (500 MG BID) WITH VIAGRA (100 MG SINGLE DOSE) RESULTED IN A 300% (4-FOLD) INCREASE IN SILDENAFIL C_{MAX} AND A 1000% (11-FOLD) INCREASE IN SILDENAFIL PLASMA AUC. AT 24 HOURS THE PLASMA LEVELS OF SILDENAFIL WERE STILL APPROXIMATELY 200 NG/ML, COMPARED TO APPROXIMATELY 5 NG/ML WHEN SILDENAFIL WAS DOSED ALONE. THIS IS CONSISTENT WITH RITONAVIR'S MARKED EFFECTS ON A BROAD RANGE OF P450 SUBSTRATES. VIAGRA HAD NO EFFECT ON RITONAVIR PHARMACOKINETICS (SEE DOSAGE AND ADMINISTRATION).

When the dose of sildenafil for subjects receiving potent CYP3A4 inhibitors was administered as recommended, the maximum free plasma sildenafil concentration did not exceed 200 nM for any individual and was consistently well tolerated.

In a study of healthy male volunteers, co-administration of the endothelin antagonist, bosentan, (an inducer of CYP3A4 [moderate], CYP2C9 and possibly of CYP2C19) at steady-state (125 mg twice a day) with sildenafil at steady-state (80 mg three times a day) resulted in 62.6% and 55.4% decrease in sildenafil AUC and C_{max} , respectively. Sildenafil increased bosentan AUC and C_{max} by 49.8% and 42%, respectively. Concomitant administration of strong CYP3A4 inducers, such as rifampin, is expected to cause greater decreases in plasma concentrations of sildenafil.

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA.

Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by non-specific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

Effects of VIAGRA on Other Drugs

***In vitro* studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 ($IC_{50} >150 \mu M$). Given sildenafil peak plasma concentrations of approximately 1 μM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

***In vivo* studies:** When VIAGRA 100 mg oral was co-administered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 8 mmHg systolic and 7 mmHg diastolic.

In three specific drug - drug interaction studies, the alpha-blocker doxazosin (4 mg and 8 mg) and sildenafil (25 mg, 50 mg, or 100 mg) were administered simultaneously to patients with benign prostatic hyperplasia (BPH) stabilized on doxazosin therapy. In these study populations, mean additional reductions of supine blood pressure of 7/7 mmHg, 9/5 mmHg, and 8/4 mmHg, and mean additional reductions of standing blood pressure of 6/6 mmHg, 11/4 mmHg, and 4/5 mmHg, respectively, were observed. When sildenafil and doxazosin

were administered simultaneously to patients stabilized on doxazosin therapy, there were infrequent reports of patients who experienced symptomatic postural hypotension. These reports included dizziness and lightheadedness, but not syncope. Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. (See section **DOSAGE AND ADMINISTRATION** and section **PRECAUTIONS**).

No significant interactions were shown when sildenafil (50 mg) was co-administered with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

Sildenafil at steady-state (80 mg three times a day) resulted in a 49.8% increase in bosentan AUC and a 42% increase in bosentan C_{max} (125 mg twice a day) (see above, **Effects of other medicinal products on sildenafil**).

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by acetyl salicylic acid (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady-state pharmacokinetics of the HIV protease inhibitors, saquinavir and ritonavir, both of which are CYP3A4 substrates.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m² basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

Pregnancy, Nursing Mothers and Pediatric Use

VIAGRA is not indicated for use in newborns, children, or women.

Pregnancy Category B: No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m² basis in a 50 kg subject. In the rat pre- and post-natal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the non-pregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

Geriatric Use: Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations**).

Effects on Ability to Drive and Use Machines

As dizziness and altered vision were reported in clinical trials with sildenafil, patients should be aware of how they react to sildenafil, before driving or operating machinery. The effect of sildenafil on the ability to drive and use machinery has not been studied.

ADVERSE REACTIONS

Pre-marketing Experience:

VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not significantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature.

In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies.

When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

TABLE 2. ADVERSE EVENTS REPORTED BY $\geq 2\%$ OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA	PLACEBO
	N=734	N=725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	2%
Abnormal Vision [†]	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

[†]Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of $>2\%$, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in $<2\%$ of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

Adverse reactions reported in clinical trials and post-marketing surveillance are presented in Table 3 below:

Table 3: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common $\geq 1/10$	Common $\geq 1/100$ to $<1/10$	Uncommon $\geq 1/1,000$ to $<1/100$	Rare $\geq 1/10,000$ to $<1/1,000$
Infections and infestations			Rhinitis	
Immune system disorders			Hypersensitivity	

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Nervous system disorders	Headache	Dizziness	Somnolence	Seizure*; Seizure recurrence*; Syncope
Eye disorders		Vision blurred; Visual disturbance; Cyanopsia	Eye pain; Photophobia; Photopsia; Chromatopsia; Ocular hyperaemia; Visual brightness	Eye oedema; Eye swelling; Dry eye; Asthenopia; Halo vision; Xanthopsia; Erythroptosis; Eye disorder; Conjunctival hyperaemia; Eye irritation; Abnormal sensation in eye; Eyelid oedema
Cardiac disorders			Tachycardia; Palpitations	
Vascular disorders		Hot flush; Flushing	Hypotension	
Respiratory, thoracic and mediastinal disorders		Nasal congestion	Epistaxis; Sinus congestion	Throat tightness; Nasal dryness; Nasal oedema
Gastrointestinal disorders		Nausea; Dyspepsia	Gastro oesophageal reflux disease; Vomiting; Abdominal pain upper; Dry mouth	Hypoaesthesia oral
Skin and subcutaneous tissue disorders			Rash	
Musculoskeletal and connective tissue disorders			Myalgia; Pain in extremity	
Reproductive system and breast disorders				Priapism*; Erection increased
General disorders and administration site conditions			Feeling hot	Irritability
Investigations			Heart rate increased	

*ADR identified post-marketing

Body as a Whole: face oedema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, allergic reaction, chest pain, accidental injury.

Cardiovascular: angina pectoris, AV block, migraine, syncope, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

Digestive: glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, liver function tests abnormal, rectal hemorrhage, gingivitis.

Hemic and Lymphatic: anemia and leukopenia.

Metabolic and Nutritional: thirst, oedema, gout, unstable diabetes, hyperglycemia, peripheral oedema, hyperuricemia, hypoglycemic reaction, hypernatremia.

Musculoskeletal: arthritis, arthrosis, tendon rupture, tenosynovitis, bone pain, myasthenia, synovitis.

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, abnormal dreams, reflexes decreased, hypesthesia.

Respiratory: asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

Skin and Appendages: urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

Special Senses: mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, cataract.

Urogenital: cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital oedema and anorgasmia.

Post-marketing Experience:

Eye disorders: red eyes/bloodshot eyes

Other events

Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include:

Nervous: anxiety.

Urogenital: prolonged erection and hematuria.

Special Senses: diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular

pressure, retinal vascular disease or bleeding, vitreous detachment/traction, and paramacular oedema.

OVERDOSAGE

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates and severities were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

DOSAGE AND ADMINISTRATION

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

THE FOLLOWING FACTORS ARE ASSOCIATED WITH INCREASED PLASMA LEVELS OF SILDENAFIL: AGE >65 (40% INCREASE IN AUC), HEPATIC IMPAIRMENT (E.G., CIRRHOSIS, 80%), SEVERE RENAL IMPAIRMENT (CREATININE CLEARANCE <30 ML/MIN, 100%), AND CONCOMITANT USE OF POTENT CYTOCHROME P450 3A4 INHIBITORS [KETOCONAZOLE, ITRACONAZOLE, ERYTHROMYCIN (182%), SAQUINAVIR (210%)]. SINCE HIGHER PLASMA LEVELS MAY INCREASE BOTH THE EFFICACY AND INCIDENCE OF ADVERSE EVENTS, A STARTING DOSE OF 25 MG SHOULD BE CONSIDERED IN THESE PATIENTS.

RITONAVIR GREATLY INCREASED THE SYSTEMIC LEVEL OF SILDENAFIL IN A STUDY OF HEALTHY, NON-HIV INFECTED VOLUNTEERS (11-FOLD INCREASE IN AUC, SEE DRUG INTERACTIONS.) BASED ON THESE PHARMACOKINETIC DATA, IT IS RECOMMENDED NOT TO EXCEED A MAXIMUM SINGLE DOSE OF 25 MG OF VIAGRA IN A 48-HOUR PERIOD.

VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

Simultaneous administration of VIAGRA doses above 25 mg and an alpha-blocker may lead to symptomatic hypotension in some patients. Doses of 50 mg or 100 mg of VIAGRA

should not be taken within 4 hours of alpha-blocker administration. A 25 mg dose of VIAGRA may be taken at any time.

SUPPLY

VIAGRA® is available as:

VIAGRA® film-coated tablets 25 mg, box, contains 1 blister @ 4 tablets.

Reg. No. DKXXXXXXXXXXXX

STORE BELOW 30°C.

HARUS DENGAN RESEP DOKTER

Manufactured by:

Fareva Amboise, Pocé-sur-Cisse, France

Imported by:

PT Ferron Par Pharmaceuticals, Bekasi, Indonesia

Marketed by:

PT Aurogen Pharma Indonesia, Jakarta, Indonesia

Brosur kemasan: Informasi untuk pasien

Tablet VIAGRA® 25 mg Sildenafil sitrat

Baca seluruh bagian brosur ini dengan cermat sebelum Anda mulai meminum obat ini karena berisi informasi penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam leaflet ini. Lihat bagian 4.

Isi leaflet ini

1. Apa itu VIAGRA® dan apa kegunaannya
2. Apa yang perlu Anda ketahui sebelum meminum VIAGRA®
3. Bagaimana cara meminum VIAGRA®
4. Kemungkinan efek samping
5. Bagaimana cara menyimpan VIAGRA®
6. Isi kemasan dan informasi lainnya

1. Apa itu VIAGRA® dan apa kegunaannya

VIAGRA® mengandung zat aktif sildenafil yang termasuk dalam kelompok obat penghambat fosfodiesterase tipe 5 (PDE 5). Obat ini bekerja dengan cara membantu merelaksasi pembuluh darah pada penis Anda, sehingga melancarkan aliran darah ke penis saat Anda terangsang secara seksual. VIAGRA® hanya akan membantu Anda untuk mengalami ereksi jika Anda dirangsang secara seksual.

VIAGRA® adalah pengobatan bagi laki-laki dewasa yang mengalami disfungsi ereksi, atau terkadang dikenal dengan istilah impotensi. Ini adalah kondisi saat seorang laki-laki tidak dapat mengalami atau mempertahankan ereksi penis yang keras yang dibutuhkan untuk aktivitas seksual.

2. Apa yang perlu Anda ketahui sebelum meminum VIAGRA®

Jangan meminum VIAGRA®

- Jika Anda alergi terhadap sildenafil atau bahan lainnya dalam obat ini (dicantumkan di bagian 6).
- Jika Anda sedang meminum obat golongan nitrat, sebab kombinasi keduanya dapat menyebabkan penurunan tekanan darah yang membahayakan. Konsultasikan dengan dokter jika Anda sedang meminum salah satu obat ini yang umumnya diberikan untuk meringankan angina pectoris (atau “nyeri dada”). Jika Anda tidak yakin, tanyakan kepada dokter atau apoteker.
- Jika Anda menggunakan obat apa pun yang dikenal sebagai donor nitrit oksida seperti amil nitrit (“poppers”), karena kombinasinya juga dapat menyebabkan penurunan tekanan darah yang berpotensi membahayakan.

- Jika Anda sedang meminum riociguat. Obat ini digunakan untuk mengobati hipertensi paru (yaitu tekanan darah tinggi dalam paru-paru) dan hipertensi paru tromboemboli kronis (yaitu tekanan darah tinggi dalam paru-paru akibat dari adanya bekuan darah). Penghambat PDE5, seperti Viagra telah terbukti mampu meningkatkan efek hipotensif dari obat ini. Jika Anda sedang meminum riociguat atau merasa ragu, konsultasikan dengan dokter Anda.
- Jika Anda mengalami gangguan jantung atau hati berat.
- Jika Anda baru-baru ini mengalami stroke atau serangan jantung, atau jika Anda memiliki tekanan darah rendah.
- Jika Anda memiliki penyakit mata turunan tertentu yang langka (seperti *retinitis pigmentosa*).
- Jika penglihatan Anda pernah hilang dikarenakan neuropati optik iskemik anterior non-arteritis (NAION).

Peringatan dan langkah-langkah pencegahan

Konsultasikan dengan dokter, apoteker, atau perawat Anda sebelum meminum VIAGRA®

- Jika Anda menderita anemia sel bulan sabit (bentuk sel darah merah yang tidak normal), leukemia (kanker darah), mieloma multipel (kanker sumsum tulang belakang).
- Jika Anda memiliki perubahan bentuk penis atau Penyakit Peyronie.
- Jika Anda memiliki gangguan jantung. Dokter Anda harus memeriksa dengan saksama apakah jantung Anda mampu menerima ketegangan tambahan akibat aktivitas seksual.
- Jika saat ini Anda mengalami tukak lambung atau gangguan perdarahan (seperti hemofilia).
- Jika Anda mengalami penurunan atau hilangnya penglihatan secara tiba-tiba, hentikan meminum VIAGRA® dan hubungi dokter Anda segera.

Anda tidak boleh menggunakan VIAGRA® bersama pengobatan oral atau lokal lainnya yang ditujukan untuk disfungsi ereksi.

Anda tidak boleh menggunakan VIAGRA bersama obat untuk hipertensi arteri pulmonal (PAH) yang mengandung sildenafil atau penghambat PDE5 lainnya.

Anda tidak boleh meminum VIAGRA® jika Anda tidak mengalami disfungsi ereksi.

Anda tidak boleh meminum VIAGRA® jika Anda adalah seorang perempuan.

Pertimbangan khusus untuk pasien dengan gangguan ginjal atau hati

Anda harus memberi tahu dokter Anda jika Anda memiliki gangguan ginjal atau hati. Dokter Anda dapat menentukan dosis yang lebih rendah bagi Anda.

Penggunaan pada anak-anak dan bayi baru lahir

VIAGRA® tidak boleh diberikan kepada pasien di bawah usia 18 tahun.

Obat-obatan lain dan VIAGRA®

Beri tahu dokter atau apoteker Anda jika Anda sedang, belum lama ini, atau akan menggunakan obat lain.

Tablet VIAGRA® dapat mengganggu kerja sejumlah obat, khususnya obat-obatan yang digunakan untuk mengatasi nyeri dada. Dalam situasi darurat medis, Anda harus menyampaikan kepada dokter, apoteker, atau perawat Anda bahwa Anda telah meminum VIAGRA® beserta waktu Anda

meminumnya. Jangan minum VIAGRA[®] bersama obat-obatan lain kecuali dokter Anda membolehkannya.

Anda tidak boleh minum VIAGRA[®] jika Anda sedang minum obat dari golongan nitrat, karena kombinasi obat-obatan ini dapat menyebabkan penurunan tekanan darah yang membahayakan. Konsultasikan selalu dengan dokter, apoteker, atau perawat Anda jika Anda sedang minum obat-obatan yang sering digunakan untuk meringankan angina pektoris (atau "nyeri dada").

Anda tidak boleh minum VIAGRA[®] jika Anda menggunakan obat apa pun yang dikenal sebagai donor nitrit oksida seperti amil nitrit ("poppers"), karena kombinasinya juga dapat menyebabkan penurunan tekanan darah yang berpotensi membahayakan.

Jika Anda sedang minum obat yang dikenal sebagai penghambat protease, seperti untuk pengobatan HIV, dokter Anda mungkin akan memulai dengan memberikan dosis VIAGRA[®] paling rendah (25 mg) kepada Anda.

Beberapa pasien yang menggunakan terapi pemblokir-alfa untuk mengobati tekanan darah tinggi atau pembesaran prostat mungkin mengalami pening atau kepala terasa ringan-, yang mungkin disebabkan oleh rendahnya tekanan darah saat duduk atau berdiri dengan cepat. Sejumlah pasien tertentu mengalami gejala ini saat minum VIAGRA[®] bersama pemblokir-alfa. Kondisi ini kemungkinan terjadi dalam waktu 4 jam setelah minum VIAGRA[®]. Untuk mengurangi peluang munculnya gejala ini, Anda harus minum dosis harian pemblokir-alfa secara rutin sebelum Anda mulai minum VIAGRA[®]. Dokter Anda mungkin akan memulai dengan memberikan dosis VIAGRA[®] yang lebih rendah (25 mg).

VIAGRA[®] dengan makanan dan alkohol

VIAGRA[®] dapat diminum dengan atau tanpa makanan. Namun demikian, VIAGRA mungkin membutuhkan waktu yang lebih lama untuk mulai bekerja jika Anda mengonsumsi makanan berlemak tinggi.

Meminum alkohol dapat menimbulkan gangguan sementara terhadap kemampuan Anda untuk mengalami ereksi. Untuk mendapatkan manfaat obat maksimum, Anda disarankan untuk tidak mengonsumsi alkohol dalam jumlah besar sebelum minum VIAGRA[®].

Kehamilan, menyusui, dan kesuburan

VIAGRA[®] tidak diindikasikan untuk digunakan oleh perempuan.

Mengemudi dan menjalankan mesin

VIAGRA[®] dapat menyebabkan pening dan memengaruhi penglihatan. Anda harus mengetahui bagaimana tubuh Anda bereaksi terhadap VIAGRA[®] sebelum Anda mengemudi atau menjalankan mesin.

3. Bagaimana cara minum VIAGRA[®]

Selalu minum obat ini dengan tepat sesuai anjuran dokter atau apoteker Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin. Dosis permulaan yang disarankan adalah 50 mg.

Anda tidak boleh minum VIAGRA[®] lebih dari satu kali sehari.

Jangan minum tablet salut selaput VIAGRA[®] bersama dengan tablet orodispersibel VIAGRA[®].

Anda dapat minum VIAGRA[®] sekitar satu jam sebelum aktivitas seksual yang Anda rencanakan. Telan tablet secara utuh bersama segelas air.

Jika Anda merasa bahwa efek VIAGRA® terlalu kuat atau terlalu lemah, konsultasikan dengan dokter atau apoteker Anda.

VIAGRA® hanya akan membantu Anda untuk mengalami ereksi jika Anda dirangsang secara seksual. Lamanya waktu yang diperlukan oleh VIAGRA® untuk bekerja berbeda-beda pada tiap orang, tetapi normalnya diperlukan waktu antara setengah hingga satu jam. VIAGRA mungkin membutuhkan waktu yang lebih lama untuk bekerja jika Anda mengonsumsi makanan berlemak tinggi.

Jika VIAGRA® tidak dapat membantu Anda untuk mengalami ereksi, atau jika ereksi Anda tidak berlangsung lama untuk menuntaskan hubungan seksual Anda, Anda harus mengonsultasikannya dengan dokter Anda.

Jika Anda meminum VIAGRA® melebihi yang seharusnya:

Anda mungkin mengalami peningkatan efek samping beserta tingkat keparahannya. Dosis di atas 100 mg tidak meningkatkan efikasi.

Anda tidak boleh meminum tablet melebihi jumlah yang disarankan dokter Anda.

Hubungi dokter jika Anda meminum tablet melebihi jumlah yang seharusnya.

Jika Anda memiliki pertanyaan lebih lanjut mengenai kegunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Kemungkinan efek samping

Seperti halnya obat-obatan lainnya, obat ini dapat menyebabkan efek samping kendati tidak semua orang mengalaminya. Efek samping yang dilaporkan berkaitan dengan penggunaan VIAGRA® biasanya tergolong ringan hingga sedang dan hanya berlangsung dalam waktu singkat.

Jika Anda mengalami efek samping serius berikut ini, hentikan meminum VIAGRA® dan dapatkan pertolongan medis segera:

- Reaksi alergi – tidak umum terjadi (dapat dialami hingga 1 antara 100 orang)
Gejalanya meliputi mengi secara tiba-tiba, kesulitan bernapas atau pening, pembengkakan kelopak mata, wajah, bibir, atau tenggorokan.
- Nyeri dada – tidak umum terjadi
Jika hal ini terjadi selama atau sesudah berhubungan badan:
- Posisikan badan Anda setengah duduk dan cobalah untuk rileks.
- **Jangan gunakan nitrat** untuk mengobati nyeri dada.
- Ereksi yang berkepanjangan dan kadang-kadang menyakitkan – jarang terjadi (dapat dialami hingga 1 di antara 1000 orang)
Jika Anda mengalami ereksi yang berlangsung lebih dari 4 jam, Anda harus segera menghubungi dokter.
- Penurunan atau hilangnya penglihatan secara tiba-tiba – jarang terjadi
- Reaksi kulit serius – jarang terjadi
Gejala-gejalanya dapat meliputi pengelupasan dan pembengkakan kulit yang parah, lepuh pada mulut, alat kelamin, dan di sekitar mata, demam.

- Kejang yang **jarang** terjadi

Efek samping lain:

Sangat umum (dapat dialami lebih dari 1 di antara 10 orang): sakit kepala

Umum (dapat dialami hingga 1 di antara 10 orang): pening, penglihatan kabur, gangguan visual, sianopsia, *hot flush* (gejala termasuk rasa panas yang muncul tiba-tiba di sekitar bagian atas tubuh anda), muka memerah, hidung tersumbat, mual, perasaan tidak nyaman atau nyeri perut bagian atas.

Tidak umum (dapat dialami hingga 1 di antara 100 orang): rhinitis, hipersensitivitas, somnolen, nyeri mata, fotopobia, fotopsia, kromatopsia, hiperemia okular, *visual brightness*, takikardia, palpitasi, hipotensi, epistaksis, kongesti sinus, penyakit refluks gastro esofageal, muntah, nyeri perut atas, mulut kering, ruam, mialgia, nyeri pada anggota gerak, perasaan panas, peningkatan denyut jantung

Langka (dapat dialami hingga 1 di antara 1.000 orang): kejang, kejang kambuhan, pingsan, edema mata, pembengkakan mata, mata kering, astenopia, halo/pelangi saat melihat cahaya, xanthopsia, eritropsia, gangguan mata, hiperemia konjungtiva, iritasi mata, sensasi abnormal pada mata, edema kelopak mata, ketidaknyamanan pada tenggorokan, rasa kering pada hidung, edema hidung, hipostesia oral, priapismus, peningkatan ereksi, iritabilitas

Jika Anda mengalami efek samping mana pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini.

5. Cara menyimpan VIAGRA®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan menyimpannya di atas suhu 30 °C.

Jangan gunakan obat ini setelah melewati tanggal kedaluwarsanya yang tercantum pada karton atau kemasan blister. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Simpan dalam kemasan aslinya untuk melindunginya dari kelembapan.

Jangan membuang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan VIAGRA®

- Zat aktif dalam obat ini adalah sildenafil. Setiap tablet mengandung sildenafil 25 mg (sebagai garam sitrat).
- Bahan lainnya adalah:
 - Inti tablet: mikrokristalin selulosa, kalsium hidrogen fosfat (anhidrat), kroskarmelosa natrium, magnesium stearat
 - Salut selaput: hipromelosa, titanium dioksida (E171), laktosa, triasetin, indigo carmine aluminium lake (E132)

VIAGRA® tablet salut selaput 25 mg, boks, berisi 1 blister @ 4 tablet.
No. Reg. DKIXXXXXXXXXXXXX.

HARUS DENGAN RESEP DOKTER

Bentuk sediaan dan isi kemasan VIAGRA®

Tablet salut selaput VIAGRA® berwarna biru dengan bentuk belah ketupat bersudut tumpul. Tablet bertuliskan “VIAGRA” pada satu sisi dan “VGR 25” pada sisi lainnya. Tablet tersedia dalam kemasan blister yang berisi 4 tablet. Ukuran kemasan tertentu mungkin tidak dipasarkan di negara Anda.

Diproduksi oleh:

Fareva Amboise, Pocé-sur-Cisse, Perancis

Diimpor oleh:

PT Ferron Par Pharmaceuticals, Bekasi, Indonesia

Dipasarkan oleh:

PT Aurogen Pharma Indonesia, Jakarta, Indonesia