Viagra

When a man is sexually excited, the penis rapidly fills with more blood than usual. The penis then expands and hardens. This is called an erection. After the man has finished having sex, this extra blood flows out of the penis back into the body. The erection goes away.

Some conditions and medicines interfere with this natural erection process. The penis cannot fill with enough blood. The man cannot have an erection. This is called erectile dysfunction if it becomes a frequent problem.

During sex, your heart works harder. Therefore sexual activity may not be advisable for people who have heart problems. Before you start any treatment for erectile dysfunction, check whether your heart is healthy enough to handle the extra strain of having sex. If you have chest pains, dizziness or nausea during sex, stop having sex and immediately medical assistance for this problem.

VIAGRA enables many men with erectile dysfunction to respond to sexual stimulation. When a man is sexually excited, VIAGRA helps the penis fill with enough blood to cause an erection. After sex is over, the erection goes away.

Sildenafil citrate, sold as **Viagra**, **Revatio** and under various other trade names, is a drug used to treat erectile dysfunction (male impotence) and pulmonary arterial hypertension (PAH). It acts by inhibiting cGMP specific phosphodiesterase type 5, an enzyme that regulates blood flow in the penis. Since becoming available in 1998, sildenafil has been the prime treatment for erectile dysfunction.

Mechanism of action

The mechanism of action of Sildenafil citrate involves the release of nitric oxide (NO) in the corpus cavernosum of the penis. NO binds

to the receptors of the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilation) of the intimal cushions of the helicine arteries, resulting in increased inflow of blood and an erection.

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil is similar to that of cGMP and acts as a competitive binding agent of PDE5 in the corpus cavernosum, resulting in more cGMP and better erections. Without sexual stimulation, and therefore lack of activation of the NO/cGMP system, sildenafil should not cause an erection.

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.

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*.

Other drugs that operate by the same mechanism include tadalafil (Cialis) and vardenafil (Levitra).

Pharmacokinetics and Metabolism

VIAGRA is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. 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 nonspecific CYP inhibitor, cimetidine, is associated with increased plasma levels of sildenafil. Both sildenafil and the metabolite have terminal half lives of about 4 hours.

Absorption and Distribution:

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 Tmax of 60 minutes and a mean reduction in Cmax of 29%.

Avoid eating grapefruit or drinking grapefruit juice while you are being treated with this medication.

The mean steady state volume of distribution (Vss) 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. 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.

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.

Geriatrics:

Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil, with free plasma concentrations approximately 40% greater than those seen in healthy younger volunteers (18-45 years).

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, 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.

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 at doses of 25 mg, 50 mg and 100 mg 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, 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. 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.

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.

Uses

Sexual dysfunction

The primary indication of sildenafil is treatment of erectile dysfunction (inability to sustain a satisfactory erection to complete intercourse). It use is now standard treatment for erectile dysfunction in all settings, including diabetes.

People on antidepressants may experience sexual dysfunction, either as a result of their illness or as a result of their treatment. A 2003 study showed that sildenafil improved sexual function in men in this situation. Following up to earlier reports from 1999, the same researchers found that sildenafil was able to improve sexual function in female patients on antidepressants as well.

Pulmonary hypertension

As well as erectile dysfunction, sildenafil citrate is also effective in the rare disease pulmonary arterial hypertension (PAH). It relaxes the arterial wall, leading to decreased pulmonary arterial resistance and pressure. This in turn reduces the workload of the right ventricle of the heart and improves symptoms of right-sided heart failure. Because PDE-5 is primarily distributed within the arterial wall smooth muscle of the lungs and penis, sildenafil acts selectively in

both these areas without inducing vasodilation in other areas of the body. Sildenafil joins bosentan and prostacyclin-based therapies for this condition.

Altitude sickness

Sildenafil has been shown to be useful for the prevention and treatment of High altitude pulmonary edema associated with altitude sickness such as that suffered by mountain climbers. While this effect has only recently been discovered, sildenafil is already becoming an accepted treatment for this condition, particularly in situations where the standard treatment of rapid descent has been delayed for some reason.

Use in sports

Professional sports players have been using drugs such as Viagra thinking that the opening of their blood vessels will enrich their muscles, therefore enhancing their performance.

Non-medical use

Recreational use

Viagra's popularity with young adults has increased over the years. It is sometimes used recreationally, though this use is somewhat pointless in young, healthy men, as they receive no benefit from the drug. Some users mix Viagra with methylenedioxymethamphetamine (MDMA, ecstasy) or other stimulants in an attempt to compensate for the side effect common to many amphetamines of erectile dysfunction, a combination known as "sextasy", "rocking & rolling", or "trail mixing". Mixing with amyl nitrite is particularly dangerous, and is potentially fatal.

Prevention of plant wilting

A low-concentration solution of sildenafil in water significantly prolongs the time before cut flowers wilt; one experiment showed a doubling in time from one week to two weeks. The mechanism of action is similar to that in humans: nitric oxide leads to the production of cGMP whose degradation by PDE5 is inhibited by sildenafil.

Jet lag research

The 2007 Ig Nobel Prize in Aviation went to Patricia V. Agostino, Santiago A. Plano and Diego A. Golombek of Universidad Nacional de Quilmes, Argentina, for their discovery that Viagra aids jet lag recovery in hamsters. Their research was published in the Proceedings of the National Academy of Sciences.

Recommended dosage

The dose of sildenafil for erectile dysfunction is 25 mg to 100 mg taken not more than once per day between 30 minutes and 4 hours prior to sexual intercourse. It is usually recommended to start with a dosage of 50 mg (or even 25 mg) and then lower or raise the dosage as appropriate. 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.**

Viagra causes erections only during sexual excitement. It does not work in the absence of arousal.

If you are over 65, have liver or kidney problems, or are taking erythromycin, ketoconazole, itraconazole, ritonavir, or saquinavir a dose of 25 milligrams may be sufficient.

Taking Viagra approximately 1 hour before sexual activity works best for most men. Depending on how and when the drug works for you, an interval of one-half hour to as much as 4 hours may prove ideal. Viagra is *not* for regular use. Take it only before sexual activity.

Sildenafil is metabolised by liver enzymes and excreted by both the liver and kidneys. **If taken with a high-fat meal, absorption is reduced**; the time taken to reach the maximum plasma concentration increases by around one hour, and the maximum concentration itself is decreased by nearly one-third.

Side effects

Like all medicines, VIAGRA can cause some side effects. These effects are usually mild to moderate and usually do not last longer than a few hours. Some of these side effects are more likely to occur with higher doses.

The most common side effects of VIAGRA are headache, flushing of the face, and upset stomach. Less common side effects that may occur are temporary changes in color vision (such as trouble telling the difference between blue and green objects or having a blue color tinge to them), eyes being more sensitive to light, or blurred vision.

In rare instances, men taking PDE5 inhibitors (oral erectile dysfunction medicines, including VIAGRA) reported a sudden decrease or loss of vision in one or both eyes. It is not possible to determine whether these events are related directly to these medicines, to other factors such as high blood pressure or diabetes, or to a combination of these. If you experience sudden decrease or loss of vision, stop taking PDE5 inhibitors, including VIAGRA, and call a doctor right away.

In rare instances, men have reported an erection that lasts many hours. You should call a doctor immediately if you ever have an erection that lasts more than 4 hours. If not treated right away, permanent damage to your penis could occur.

Sudden loss or decrease in hearing, sometimes with ringing in the ears and dizziness, has been rarely reported in people taking PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the PDE5 inhibitors, to other diseases or medications, to other factors, or to a combination of factors. If you experience these symptoms, stop taking VIAGRA and contact your doctor right away.

In clinical trials, the most common adverse effects of sildenafil use included headache, flushing, dyspepsia, nasal congestion and impaired vision, including photophobia and blurred vision. Some sildenafil users have complained of seeing everything tinted blue (cyanopsia). Some complained of blurriness and loss of peripheral vision. In May 2005, the U.S. Food and Drug Administration found that sildenafil could lead to vision impairment and a number of studies have linked sildenafil use with nonarteritic anterior ischemic optic neuropathy.

Rare but serious adverse effects found through postmarketing surveillance include priapism, severe hypotension, myocardial infarction (heart attack), ventricular arrhythmias, stroke, increased intraocular pressure and sudden hearing loss. In October 2007, the FDA announced that the labeling for all PDE5 inhibitors, including sildenafil, required a more prominent warning of the potential risk of sudden hearing loss as the result of these postmarketing reports.

Care should be exercised by patients who are also taking protease inhibitors for the treatment of HIV. Protease inhibitors inhibit the metabolism of sildenafil, effectively multiplying the plasma levels of sildenafil, increasing the incidence and severity of side-effects. It is recommended that patients using protease inhibitors limit their use of sildenafil to no more than one 25 mg dose every 48 hours.

Concomitant use of sildenafil and an alpha blocker may lead to low blood pressure, but this effect does not occur if they are taken at least four hours apart.

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 8.4/5.5 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 25 mg, 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.

Side effects cannot be anticipated. If any develop or change in intensity, inform your doctor as soon as possible. Only your doctor can determine if it is safe for you to continue taking Viagra.

More common side effects may include:

Abnormal vision (color tinge, blurring, sensitivity to light), acid indigestion, diarrhea, flushing, headache, nasal congestion, urinary tract infection

Heart attack, stroke, heart irregularities, dangerous surges in blood pressure, and sudden death have all been reported after use of Viagra, usually in men with existing cardiac risk factors, and typically during or shortly after sex.

A serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction include: rash, itching, unusual swelling, severe dizziness, trouble breathing. If Viagra gives you an allergic reaction, do not use it again.

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.

Do not take this medication with any other product that contains sildenafil or other similar medications for erection problems (e.g., tadalafil, vardenafil).

Caution is advised when using this drug in the elderly because they may be more sensitive to the side effects of the drug.

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:

Caution is advised when Phosphodiesterase Type 5 (PDE5) inhibitors are co-administered with alpha-blockers. PDE5 inhibitors, including VIAGRA, and alpha-adrenergic blocking agents are both vasodilators with blood pressure lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients, concomitant use of these two drug classes can lower blood pressure significantly leading to symptomatic hypotension (e.g. dizziness, lightheadedness, fainting).

Consideration should be given to the following:

- Patients should be stable on alpha-blocker therapy prior to initiating a PDE5 inhibitor. Patients who demonstrate hemodynamic instability on alpha-blocker therapy alone are at increased risk of symptomatic hypotension with concomitant use of PDE5 inhibitors.

- In those patients who are stable on alpha-blocker therapy, PDE5 inhibitors should be initiated at the lowest dose.

- In those patients already taking an optimized dose of a PDE5 inhibitor, alpha-blocker therapy should be initiated at the lowest dose. Stepwise increase in alpha-blocker dose may be associated with further lowering of blood pressure when taking a PDE5 inhibitor.

- Safety of combined use of PDE5 inhibitors and alpha-blockers may be affected by other variables, including intravascular volume depletion and other anti-hypertensive drugs.

Viagra has systemic vasodilatory properties and may augment the blood pressure lowering effect of other anti-hypertensive medications.

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.

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).

In humans, VIAGRA has no effect on bleeding time when taken alone or with aspirin. *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.

Physician should advise patients to stop taking PDE5 inhibitors, including VIAGRA, and seek prompt medical attention in the event of sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including VIAGRA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors

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

Special warnings about Sildenafil citrate

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. **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.**

If you have heart problems severe enough to make sexual activity a danger, you should avoid using Viagra. Use it cautiously--if at all--if you have had a heart attack, stroke, or life-threatening heart irregularities within the past 6 months. Be equally cautious if you have severe high or low blood pressure, heart failure, or unstable angina (crushing heart pain that occurs at any time).

If you take Viagra and develop cardiac symptoms (for example, dizziness, nausea, and chest pain) during sexual activity, do not continue. Alert your doctor to the problem as soon as possible. If you have a condition that might result in long-lasting erections, such as sickle cell anemia, multiple myeloma (a disease of the bone marrow), or leukemia, use Viagra with caution. Also use cautiously if you have a genital problem or deformity such as Peyronie's disease. If an erection lasts more than 4 hours, seek treatment immediately. Permanent damage and impotence could result.

If you have a bleeding disorder, a stomach ulcer, or the inherited eye condition known as retinitis pigmentosa, use Sildenafil citrate with caution. Its safety under these circumstances has not yet been studied. The safety of VIAGRA is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Do not take Viagra if you are taking any nitrate-based drug, including nitroglycerin patches (Nitro-Dur, Transderm-Nitro), nitroglycerin ointment (Nitro-Bid, Nitrol), nitroglycerin pills (Nitro-Bid, Nitrostat), and isosorbide pills (Dilatrate-SR, Isordil, Sorbitrate). Combining Viagra with these drugs can cause a severe drop in blood pressure.

To avoid low blood pressure, do not take the 50-milligram or 100-milligram dose of Viagra within 4 hours of taking an alpha-blocking drug such as Cardura.

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.

Remember that Viagra offers no protection from transmission of sexually transmitted diseases, such as HIV, the virus that causes AIDS.

Possible food and drug interactions when taking Sildenafil citrate

This drug should not be used with the following medications because very serious (possibly fatal) interactions may occur: nitrates (e.g., nitroglycerin, isosorbide), nitroprusside (or any "nitric oxide donor" drugs), recreational drugs called “poppers” containing amyl or butyl nitrite.

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.

When VIAGRA is co-administered with an alpha-blocker, patients should be stable on alpha- blocker therapy prior to initiating VIAGRA treatment and VIAGRA should be initiated at the lowest dose.

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

If Viagra is taken with certain other drugs, the effects of either could be increased, decreased, or altered. It is especially important to check

with your doctor before combining Viagra with the following:

Other impotence remedies including Caverject and Muse
Alpha-blockers such as doxazosin (Cardura)
Amlodipine (Norvasc)
Cimetidine (Tagamet)
Erythromycin (E-Mycin, Ery-Tab, PCE)
Itraconazole (Sporanox)
Ketoconazole (Nizoral)
Nitrates such as Isordil, Nitro-Bid, and Nitro-Dur
Rifampin (Rifadin, Rimactane)
Ritonavir (Norvir)
Saquinavir (Fortovase, Invirase)

Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use, especially of: alpha-blocker medication (e.g., doxazosin, prazosin, terazosin), other medications for impotence, bosentan, high blood pressure medicines, drugs affecting liver enzymes that remove sildenafil from your body (such as azole antifungals including ketoconazole/itraconazole, macrolide antibiotics including erythromycin, cimetidine, delavirdine, rifamycins including rifabutin/rifampin, St. John's wort, certain anti-seizure medicines including carbamazepine).

If you are taking an HIV protease inhibitor (e.g., ritonavir, saquinavir), do not take more than a 25mg dose of sildenafil in a 48 hour period.

If you are taking more than a 25mg dose of sildenafil and are also taking an alpha-blocker medication (e.g., doxazosin, prazosin, terazosin) for various conditions (e.g., enlarged prostate), separate the time between taking these medications by more than 4 hours.

Special information if you are pregnant or breastfeeding

Viagra should not be used by women. Its affects during pregnancy and breastfeeding have not been studied. VIAGRA is not indicated for use in newborns, children.

To avoid low blood pressure, do not take the 50-milligram or 100-milligram dose of Viagra within 4 hours of taking an alpha-blocking drug such as Cardura.

Overdosage

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.

No overdose of Viagra has been reported. However, any medication taken in excess can have serious consequences. If you suspect an overdose, seek medical attention immediately.