ERECTILE DYSFUNCTION
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Puncturing one's penis with a needle is not for the squeamish. Piercing the penis with a needle and then injecting a chemical to enhance one's sexual potency sounds more like a bizarre, sadomasochistic nightmare from the annals of Krafft-Ebing's *Psychopathia Sexualis* than a doctor-recommended treatment of impotence. Nevertheless, many men, with guidance from their physicians, practice self-injection of the penis to achieve an erection. Three types of medications—phentolamine (an alpha-blocker), papaverine (a smooth muscle blocker)—and prostaglandin E1—are used. These medications are effective in stimulating erections because they overcome neurologic signals that normally keep the penis in a limp or flaccid state. Neurological control of erections is vested in the sympathetic nervous system.

To understand how the sympathetic nervous system works, it is useful to create a simple scary example. Imagine, that you are alone at night walking down a dark street. There is no sound. Then, as you are absorbed with your thoughts, someone sneaks up behind you and says, "Boo!"

Your sympathetic nervous system immediately swings into action to cause, among other reactions, an increase in pulse rate and blood pressure. The change in pulse and blood pressure is caused by internally produced adrenaline like compounds with unique properties designated alpha or beta. Beta forces cause an increase in pulse rate, while alpha influences are responsible for the increase in blood pressure.

What does this have to do with erections? The penis is richly endowed with extensions of the sympathetic nervous system, specifically nerves of the alpha type. Alpha influences play a vital role as facilitators or inhibitors of normal erections.

When the alpha forces dominate, the penis remains at rest. A penile injection of a medication that blocks the alpha nerves overrides these influences and makes it possible for a full and unrestrained flow of blood to be directed into the erectile bodies of the penis. Medications like phentolamine, an alpha blocker, and prostaglandin E, a muscle relaxant with probable alpha-blocking activity, cause erections by interfering with the prevailing nerve signals that would maintain the penis in a limp state.

It is somewhat more difficult to understand exactly how papaverine works. There are no papaverine receptors in the penis. Papaverine, unlike alpha-adrenergic compounds or prostaglandins, is not made by the body. However, papaverine has one characteristic that is useful in inducing an erection: It is a smooth-muscle relaxant.

The body has two types of muscles, striated and smooth. Striated muscles are literally striped in appearance and are, for the most part, under voluntary control. The muscles of the arms, legs, and face are striated muscles. Smooth muscle— are not under volitional control. For example, the muscles in the intestines are smooth muscles. The muscles lining the penile blood vessels that must dilate for an erection to occur are also smooth muscles. It is presumed that papaverine induces an erection by causing these intrapenile smooth muscles to relax, thereby allowing or encouraging increased blood flow into the penis.

Penile Injection
To be fully effective, the medications must be injected directly into one of the penile erectile bodies, the corpora cavernosum. The medication will diffuse over to the other side of the penis so that symmetrical erection is acquired.

Method of intrapenile injection.

A cross section of the penis illustrates the corpora cavernosa surrounded by the thick outer fibrous sheath (tunica albuginea). The needle is inserted at a ninety-degree angle to the penile shaft and must penetrate the tunica albuginea to make contact with the corpus cavernosum. Patients are taught to advance the needle into the penis and wait for a slight "give" in the resistance. When they sense this change in tension, they know that they have punctured the tunica albuginea. The medicine is then injected. An erection occurs within ten to thirty minutes. Most urologists recommend that injection be performed no more than twice a week. Papaverine, phentolamine, and prostaglandin E, (marketed as alprostadil [Prostin VR Pediatric]) are available in most pharmacies, as are insulin syringes with very small needles.

Candidates for Intrapenile Injections

Sixty-five to 75 percent of impotent men can have an erection induced by the intrapenile injection of combined papaverine and phentolamine. Preliminary reports from Japan suggest that 86 percent acquire erections with prostaglandin E, alone. The men most likely to respond to injections are those with neurogenic impotence. Injection can induce erections in men with vascuogenic impotence, but only if the dose of medication is significantly greater than that needed for other men. Intrapenile injections are not an effective long-term treatment for men with vascuogenic impotence because the injections will eventually fail to stimulate erections even if a large amount of drug is used. In addition, for reasons that remain unclear, about one-third of men with psychogenic impotence do not respond adequately to intrapenile injections.
Yohimbine

Man has always been intrigued and tantalized by the fantasy of discovering an aphrodisiac, a substance that would stimulate his sexual appetite and power. Some foods and drugs are thought to be imbued with aphrodisiac properties, and those who were privy to the secret ingredients of the sexually stimulating substances were highly valued. The physician to Louis XIV slipped the monarch a special potion each night before the king received a new lady in his bedchambers. The royal physician's potions were not always effective, causing the king to become displeased, truculent, and vengeful.

At one time it was believed that the drug yohimbine had aphrodisiac properties. Certainly yohimbine had the appropriately exotic lineage to satisfy preconceptions of what an aphrodisiac should be. Yohimbine was derived from the bark of a tree that grows only in Africa. It was believed that natives boiled the tree bark in a caldron and then harvested the residue. The yohimbine extract was then administered to men and women who were said to experience a sudden and striking increase in sexual desire.

Intrigued by these descriptions, Western scientists decided to look into the effects of yohimbine in man. Yohimbine, marketed under the name of Afrodex, was tested in 10,000 impotent men. Eighty percent were said to have restoration of potency. That report was published in 1968. Immediately thereafter Afrodex vanished.

Interest in yohimbine was resurrected in the 1980s. Yohimbine, now available as the prescription drug Yocon, has been tested in one hundred impotent men. Half received yohimbine and the other half placebo. Twenty-one percent of the Yohimbine-treated patients had a complete return of sexual function. A surprising 13.8 percent of placebo-treated patients also reported a full return of sexual function. Statistical analysis indicated that yohimbine was not significantly better than placebo in restoring potency.

Was it possible that the dose of yohimbine administered was too low to have produced a positive effect on male sexual function? Apparently not. Larger doses of Yohimbine were given in another study involving eighty-two impotent men. With higher doses 14 percent reported a full return of sexual function. This figure is roughly comparable to the 13.8 percent full response in the placebo-treated patients in the prior study.

Yohimbine is an intriguing drug because it functions as an alpha-adrenergic antagonist. Drugs that block the action of alpha-adrenergic nerves have been successful in inducing erections, but only when injected directly into the penis (see chapter 13). The specific subset of alpha-adrenergic properties needed to induce an erection is unfortunately missing in yohimbine. The alpha-adrenergic properties retained by yohimbine cause blood pressure and pulse to rise, and provoke a sense of nervousness and anxiety. Current studies indicate that yohimbine is no more successful than placebo in restoring sexual function. Yohimbine has worrisome cardiovascular side effects. Placebos do not.
Other Therapies

The Vacuum Constrictor Device (VCD)

Any system encouraging blood to flow into and be captured in the penis should produce an erection. This is the principle behind the vacuum constrictor device (VCD) now offered as a noninvasive means of restoring erections for some impotent men.

Devices resembling the VCD have been shuttling in and out of favor for more than seventy years. The original concept has been traced to the inventor Otto Lederer, who in 1917 was granted a patent for a unit that would allow "persons considered completely impotent to perform sexual intercourse in a normal manner." It is not known whether the Lederer device was ever produced. A newer product, undoubtedly a variation on the original theme, was developed by a man to help him deal with his own impotence. It is marketed under the name ErecAid and sells for about $400.

There are several components to the ErecAid device (see figure 14). A cylinder designed to fit over the limp penis is connected to a hand-operated vacuum pump. Suction from the pump creates a negative pressure within the cylinder, and this encourages an increased flow of arterial blood into the penis. Venous outflow is prevented by tight bands that fit over the base of the penis. A petroleum jellylike substance lubricates the system and seals the base of the cylinder. When a user achieves an adequate erection (and with the rubber bands inhibiting venous outflow still attached), he removes the cylinder. The vacuum-induced erection is maintained for up to thirty minutes.

Some dexterity and skill are required to operate the VCD. The user must place the unit on some nearby surface while the limp penis is stuffed into the vacuum chamber. With the penis and the chamber perched at an angle, his hands are free to pump air out of the chamber and affix the restraining bands to the base of the penis. Often, significant pressure must be applied.
Three to seven minutes in the vacuum chamber are required to achieve erections of optimum rigidity.

Limitations of the VCD

Not only does vacuum-induced pressure in the VCD cause most men to experience penile discomfort, but the erection achieved by this means is inferior to a spontaneous erection in three significant aspects. Once the erection has been induced by the vacuum, the rubber bands in place at the base of the penis choke off blood flow into the penis. This causes penile skin temperatures to fall to 96°F. One-third of the female partners of men using VCDs found the chilled penis displeasing during intercourse.

Another drawback is that as the penis becomes engorged and congested by the VCD-induced suction and inhibition of venous outflow, penile circumference increases more than it would during a normal erection. This gives the penis a sausage like appearance. Third, the erection created by the VCD is rigid only from the point at which the rubber bands are affixed. This means that it is not fully upright and rigid like a normal erection, but flexible and capable of swiveling or pivoting at its base.

The VCD also does not permit normal ejaculation. Because the rubber bands remain in place throughout the sexual act, semen is trapped in the urethra and can be released only after the bands are removed. Despite these limitations, the manufacturers of the VCD say that more than 15,000 units have been sold in the United States since 1983.

Reports on Patients' Experiences

Surgical implantation of penile prosthetic devices is today a commonly accepted means of restoring erectile capability to impotent men. In 1989 U. S. surgeons implanted an estimated 27,500 penile prostheses.

Dr. William Scott of the Johns Hopkins Medical School and Dr. Michael Small, now professor of urology at the University of Miami Medical School, and his associate Dr. H. M. Carrion are recognized as the patron saints of modern penile prosthesis implant surgery. Dr. Scott fashioned an inflatable silicone penile prosthesis (IPP) that he first implanted in early 1973. Drs. Small and Carrion developed their unit shortly thereafter. The Scott and Small-Carrion devices are the prototypes for most of today's penile prostheses.

The original Scott prosthesis, a multi-component device, had a fluid reservoir implanted in the lower abdomen. A tube from this reservoir was connected to a bulb in the scrotum. The penis remained in a normal flaccid state until intercourse was desired. Then an erection was created by pumping the scrotal sac.

Types of Penile Prostheses
The Small-Carrion and Scott penile prostheses are still used but are not the only options. There are a number of different devices on the market today. Four discrete categories of prostheses—semi-rigid, malleable, inflatable, and hinged—are currently available. All the units listed below have been judged safe and effective by an expert group of urologic surgeons recruited by the American Medical Association to participate in a recent Diagnostic and Therapeutic Technology Assessment panel.

The original *Small-Carrion* prosthesis consists simply of two rigid rods. Penile prostheses with abdominal fluid reservoirs include the *Scott-AMS 700* and a similar device manufactured by the Mentor Corporation. The *Jonas* prosthesis is a semi-malleable device that depends on a network of internal silver wires to allow for some degree of flexibility.

The *OmniPhase* and *DuraPhase* prostheses have internal cables that allow the device to bend to a flaccid state when not in use. These units are activated by adjusting the cable to produce penile rigidity. Other malleable devices like the *AMS 600* and *Mentor* have similar designs. The *Finney* prosthesis is hinged and converts from flaccid to rigid state merely by locking the hinge in place. Newer inflatable prostheses like the *Hydroflex* and *FlexiFlate* have internal fluid systems and are designated as self-contained penile prostheses (SCPP). The SCPP transforms the penis from a flaccid to erect state by manipulation of a valve implanted in the tip of the penis.

Individual urologic surgeons may at one time or another favor one prosthesis over another. However, no single device has yet emerged as the dominant unit of choice. Each device has its own intrinsic advantages and disadvantages (see table 2). The rigid, malleable, hinged, and controlled expansion cylinder devices do not increase penis length or girth. These devices come in a variety of lengths, the urologist chooses from an inventory of prosthetic units a rod customized for each individual patient. The Scott and the comparable Mentor multi-component inflatable penile prostheses (IPPs) both allow some increase in penile girth and rigidity without changing penis length.
Most urologists take pains to discuss this issue in detail. It is important for potential recipients to understand this preoperatively lest they harbor any illusions of acquiring significant augmentation of penile anatomy and sexual prowess. Such fantasies can never be fulfilled by any of the currently available prosthetic devices.

How Prostheses Are Implanted

Normal erections occur as increased blood flows into and is trapped in the two corpora cavernosa and the corpus spongiosum. Penile prosthetic devices, whatever kind, all attempt to duplicate this process by outfitting the penis with silicone surrogates for the two corpora cavernosa. (The corpus spongiosum is not replaced during implant surgery.) Prior to implantation, the tissue in the penile cavernosa must be stretched to accommodate the rods. Patients receiving either the Scott or Mentor inflatable prosthesis require one additional surgical procedure. The bulb for activation or transfer of fluid from a reservoir to the prosthetic shaft is surgically implanted in the scrotum.

Most prostheses are inserted by making a surgical incision either in the lower abdomen or at the junction of the penis and the scrotum and then advancing the rod forward toward the tip of the penis. Some of the newer self-contained penile prostheses, on the other hand, may be inserted by making an incision around the tip of the penis and pushing the prosthetic rods backward toward the bony joint at the end of the torso. The patient usually requires general anesthesia and stays in the hospital three to five days. Some surgeons are giving patients a spinal block (or spinal epidural anesthesia) and sending them home on the same day, but this practice is not widespread. Inflammation, a reaction to the insertion of a foreign body in the penis, causes some postoperative pain, which is controlled by medication. The pain subsides as the inflammation wanes. Following surgery, the patient must allow four to six weeks for healing. During this interval the silicone rods become firmly embedded and anchored in the penile shaft. Then the prosthesis is ready for use.

Success Rate

Recipients of penile prostheses are generally pleased with the results. All acquire a rigidity of the penile shaft adequate for penetration. Initial reports from urologic surgeons were glowing, with success rates reported at 90 to 95 percent. Long term follow-up has tempered this enthusiasm to some degree. Today, patient and partner satisfaction is closer to 60 to 75 percent.

Complications of Penile Prosthesis Surgery

A surprisingly large number of men will require repeat surgery. The most common complications are mechanical failure of the prosthesis, postoperative infection, and penile pain. Mechanical complications occur most often in multi-component inflatable prostheses and reflect malfunction in the workings of the rods, cylinders, or hydraulic system, or kinks in the tubing. The prosthesis must be removed and replaced with either a new, identical unit or an alternative type of prosthesis; the choice is up to the urologist and patient. Postoperative
wound infection is less common today than in the past. Now implant recipients receive antibiotic treatment during and immediately after surgery.

Postoperative pain does occur in some patients. It is usually localized in the tip of the penis (the glans); however, discomfort in the penile shaft, scrotum, base of the penis, or abdomen is not uncommon. In one series of 179 penile prosthesis implants performed at the Mayo Clinic, 61 patients reported complications with the prostheses' mechanisms. Another 42 patients experienced pain, most commonly at the tip of the penis, but occasionally in the penile shaft, scrotum, base of the penis, or abdomen. Of these men, 32 rated their pain moderate or severe.

Pain can herald a more serious problem. It may imply that the position of the prosthesis compromises the function of other vital structures. Pressure on the urethra will cause pain and is a warning of some underlying problem. Paraplegic patients, however, do not perceive pain. As many as one-third of impotent paraplegic men with penile prostheses experience damage to their urethra within six months after surgery. Research indicates that complications as well as the need for re-operation seem to depend on the type of device implanted, the duration of the follow-up, and the group of patients studied. For example, patients implanted with the older, rigid Small-Carrion prosthesis rarely require re-operation. The re-operation rate is much higher with inflatable penile prostheses (IPP) (see table 3). The malleable and self-contained penile prostheses (SCPP) are the least prone to mechanical breakdown. However, these devices are relatively new, and most urologists have little more than two to three years of experience with them. Still, even within this brief time span, re-operation rates of 14 to 22 percent have been reported.

Although surgical success rates for some devices now approach 90 to 95 percent, patient satisfaction does not parallel this impressive figure. A major problem is disappointment with postoperative penile length and width. Some men never attempt intercourse after the prosthesis is implanted; others have intercourse for only a brief time and then abandon sexual activities. Additional areas of disaffection with prostheses surfaced in response to specific questions.

The majority of urologists are men, and in the beginning the male perspective distinctly covered the reported results of prosthesis surgery. Female health care professionals saw things differently. They approached the issue of satisfaction after implantation by interviewing both partners. Some couples were not having intercourse at all. Of those who were having intercourse, 25 percent reported restriction in positions because of the decreased penis size. Fifteen percent of the men experienced diminution of orgasmic intensity. Still, 79 percent of men said that they would, if given the opportunity, undergo the operation again. Only 59 percent of their partners had no hesitation.

Some urologists claim that satisfaction depends on the type of prosthesis, with IPP recipients being generally more satisfied than those who receive other prostheses. Because they are easily concealed and readily activated, one would have anticipated that the multi-component IPP would have emerged by now as the dominant, if not the only, penile prosthetic device implanted.
This has not turned out to be the case, for two reasons. Significant problems with the internal hydraulics of IPPs remain, and mechanical failures are common. Perhaps more troublesome is the fact that a certain amount of manual dexterity is required to inflate the IPP.

Originally, in an effort to mimic the genital caressing that is a natural component of sexual foreplay, the man's sexual partner was encouraged to play an active role in pumping the scrotal bulb so that fluid could be transferred from the abdominal reservoir to the prosthesis, a maneuver intended to mimic a stimulated erection. This has not been as warmly embraced as expected.

Sexual partners are often unwilling to participate in the pumping procedure. Some are simply not deft at manipulating the scrotal bulb. As a result, inadequate amounts of fluid are transferred from the reservoir to the prosthesis shaft, and a suboptimal erection ensues. In such cases failure of the device has been ascribed not to mechanical problems of the unit itself but to the inadequate level of participation of sexual partners. Those who have been unwilling to become involved as vigorous squeezers of the scrotal bulb have been decried as "timid pumpers." Other factors may also have a significant impact on postoperative sexual satisfaction.

Obese patients are often displeased following penile prosthesis surgery because the length of the unit protruding beneath their lower abdominal fat pad is limited. Most prostheses are approximately eight inches in length. If there is an extensive overhanging fat pad, then perhaps only an additional four inches of rigid penile tissue will protrude for purposes of sexual intercourse. If the patient's partner is also obese, it will be very difficult for the couple to find a position in which penile-vaginal penetration and adequate vaginal containment is possible. For obese couples, postoperative sexual gratification may be limited.

Inappropriate expectations are high on the list of reasons for postoperative patient/partner dissatisfaction. The prosthesis provides only the penile rigidity necessary to achieve vaginal penetration. Patients who anticipate that the equipment will allow them to recapture the real, or imagined, sexual prowess of their youth are likely to be displeased.

Patients whose impotence is attributed to psychogenic factors do not derive as much long-term benefit from prosthetic surgery as those whose impotence is caused by either neurogenic or vasculogenic factors.

On occasion, impotent men have sexual problems other than erectile dysfunction. Lack of spontaneous arousal, limited libido, and ejaculatory disorders are not corrected by penile prosthesis implantation.

The level of preoperative patient/partner interaction is a critical determinant in evaluating postoperative satisfaction. If, for example, the female partner has her own sexual dysfunction, such as pain during intercourse, then she may be fearful of experiencing vaginal penetration again. A man may choose to have a penile prosthetic implant without notifying his partner. Such a decision is commonly interpreted as a rejection of the partner. In addition, some women are fearful that their previously impotent partners, now outfitted with penile prostheses, will seek other lovers. Limited studies exploring this question have indicated that penile
prosthesis recipients are no more susceptible to seduction, nor do they routinely seek out new sexual opportunities more often than other comparably aged potent men.

On the other hand, some female partners of impotent men, frustrated after long periods of sexual abstinence, may pressure the men into surgery. Any discordance in patient/partner desires for penile prosthesis surgery is considered a major risk factor for postoperative dissatisfaction.

Couples who have distanced themselves sexually from each other and have ceased hugging, touching, and all sensual and erotic contact may not be able to retrieve all aspects of normal sexual function merely by placing a prosthetic rod in the penis. Clearly, satisfaction is maximal only when both partners are involved in all discussions and decisions from the beginning.

As noted, patients with Peyronie's disease have no difficulty achieving an erection. But the erection bends, so the penis deviates, often creating a J-shaped erection unsuitable for intercourse. Peyronie's disease occurs when fibrous bands grow in the outer lining of the penis and tug at the penile shaft. The bands can be removed surgically, but this is only a temporary solution because these strictures tend to recur at the same or different locations in the penis. Implanting a prosthesis is often the only way to circumvent the problem.

Men with endocrine disorders, whose potency can be restored with appropriate hormonal therapy, and men with overt psychological problems, who require psychotherapy, psychiatric medications, or both, are the only groups to whom physicians do not routinely offer penile prosthetic implants.

VIAGRA

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-propyl1H-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, 50 mg and 100 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, eroscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, 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 (>80-fold for PDE1, > 1,000fold for PDE2, PDE3, and PDE4). The approximately 4,000-fold selectivity for PDE5 versus PDE3 is important because that PDE 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; 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.

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
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%. 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 pharmacological 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.

Pharmacokinetics in Special Populations 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).

Renal Insufficiency: In volunteers with mild (CLcr=50-80 mL/min) and moderate (CLcr=30-49 mL/min) renal impairment, the pharmacokinetics of a single oral dose of VIAGRA (50 mg) were not altered. In volunteers with severe (CLcr=<30 mL/min) renal impairment, sildenafil clearance was reduced, resulting in approximately doubling of AUC and Cmax compared to age-matched volunteers with no renal impairment.

Hepatic Insufficiency: In volunteers with hepatic cirrhosis (Child-Pugh A and B), sildenafil clearance was reduced, resulting in increases in AUC (84%) and Cmax (47%) compared to age-matched volunteers with no hepatic impairment.

Therefore, age >65, hepatic impairment and severe renal impairment are associated with increased plasma levels of sildenafil. A starting oral dose of 25 mg should be considered in those patients.

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 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. Larger effects were recorded among patients receiving concomitant nitrates.

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 I; 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.

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 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, 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. 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. Sixty three percent, 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. 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...
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 (TURF) 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.

**CONTRAINDICATIONS**

Consistent with its known effects on the nitric oxide/cGMP pathway, 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). 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.

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.

VIAGRA has systemic vasodilatory properties that resulted in transient decreases in supine blood pressure in healthy volunteers (mean maximum decrease of 8.4/5.5 mmHg). 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.
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. 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 indicated.

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. Controlled studies of drug interactions between VIAGRA and other antihypertensive medications have not been performed.

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 treatments for erectile dysfunction have not been studied. Therefore, the use of such combinations is not recommended.

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.

**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.

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 1*450 (CYP) isoforms 3A4 (major route) and 2C9 (minor route). Therefore, inhibitors of these isoenzymes may reduce sildenafil clearance.

In vivo studies: Cimetidine (800 mg), a nonspecific CYP inhibitor, caused a 56% increase in plasma sildenafil concentrations when coadministered with VIAGRA (50 mg) to healthy volunteers.

When a single 100 mg dose of VIAGRA was administered with erythromycin, a specific 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 Cmax 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 coadministered with CYP3A4 inhibitors (such as ketoconazole, erythromycin, or cimetidine.

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 Cmax 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.

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 nonspecific 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 1 A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC50 >150 pM). Given sildenafil peak plasma concentrations of approximately 1 pM 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 coadministered 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.

No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (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 1821 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 MRI ID on a mg/m2 basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant 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. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be adjusted.

**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>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percentage of Patients Reporting Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIAGRA</td>
</tr>
<tr>
<td></td>
<td>N=734</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
</tr>
<tr>
<td>Flushing</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3%</td>
</tr>
<tr>
<td>Abnormal Vision*</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
</tr>
</tbody>
</table>

*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 G2% 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:

**Body as a whole:** face edema, photosensitivity reaction, shock, asthenia, pain, chills,
accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

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

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

**Hemic and Lymphatic:** anemia and leukopenia.

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

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

Nervous: ataxia, hypertonia, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, 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, dry eyes.

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

**POST-MARKETING EXPERIENCE:**
Cardiovascular Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting 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 VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors (see WARNINGS for further important cardiovascular information).

**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: seizure and anxiety.

Urogenital: prolonged erection, priapism (see WARNINGS) and hematuria.

Ocular: 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 edema.

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 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. 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.