

# Sildenafil

Chemical structure of Sildenafil

Sildenafil

Systematic (IUPAC) name

1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine citrate

Sildenafil citrate, sold under the names Viagra, Revatio and under various other names, is a drug used to treat male erectile dysfunction (impotence) and pulmonary arterial hypertension (PAH), developed by the pharmaceutical company Pfizer. Its primary competitors on the market are tadalafil (Cialis), and vardenafil (Levitra).

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## History

Sildenafil (compound UK-92,480) was synthesized by a group of pharmaceutical chemists working at Pfizer's Sandwich, Kent research facility. It was initially studied for use in hypertension (high blood pressure) and angina pectoris (a form of ischaemic cardiovascular disease). Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina, but that it could induce marked penile erections. Pfizer therefore decided to market it for erectile dysfunction, rather than for angina. The drug was patented in 1996, approved for use in erectile dysfunction by the Food and Drug Administration on March 27, 1998, becoming the first pill approved to treat erectile dysfunction in the United States, and offered for sale in the United States later that year. It soon became a great success: annual sales of Viagra in the period 1999–2001 exceeded \$1 billion.

The British press portrayed Peter Dunn and Albert Wood as the inventors of the drug, a claim which Pfizer disputes. Their names are on the manufacturing patent application drug, but Pfizer claims this is only for convenience.

Even though sildenafil is only available by prescription from a doctor, it was advertised directly to consumers on US TV (famously being endorsed by former United States Senator Bob Dole and football star Pelé). Numerous sites on the Internet offer Viagra for sale after an "online consultation", a mere web questionnaire. The "Viagra" name has become so well known that many fake aphrodisiacs now call themselves "herbal Viagra" or are presented as blue tablets imitating the shape and colour of Pfizer's product. Viagra is also informally known as "Vitamin V", "the Blue Pill", as well as various other nicknames.

In February 2007, it was announced that Boots the Chemist would trial over the counter sales of Viagra in stores in Manchester, England. Men aged between 30 and 65 would be eligible to buy four tablets after a consultation with a pharmacist.

Pfizer's worldwide patents on sildenafil citrate will expire in 2011–2013. The UK patent held by Pfizer on the use of PDE5 inhibitors (see below) as treatment of impotence was invalidated in 2000 because of obviousness; this decision was upheld on appeal in 2002.

## Mechanism of action

Part of the physiological process of erection involves the parasympathetic nervous system causing 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) in the corpus cavernosum, 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. Other drugs that operate by the same mechanism include tadalafil (Cialis®) and vardenafil (Levitra®).

Sildenafil is metabolised by hepatic enzymes and excreted by both the liver and kidneys. If taken with a high-fat meal, there may be a delay in absorption of sildenafil and the peak effect might be reduced slightly as the plasma concentration will be lowered.

### **Dosage and price**

As with all prescription drugs, proper dosage is at the discretion of a licensed medical doctor. The dose of sildenafil is 25 mg to 100 mg taken 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 and then lower or raise the dosage as appropriate. The drug is sold in three dosages (25, 50, and 100 mg), all three costing about US\$10 per pill. Name-brand Viagra sildenafil is not scored and a fairly hard coating makes it more difficult to accurately cut the pills in half, even with a pill cutter.

Viagra pills are blue and diamond-shaped with the words "Pfizer" on one side, and "VGR xx" (where xx stands for "25", "50" or "100", the dose of that pill in milligrams) on the other.

### **Contraindications**

#### **Contraindications include:**

- \* When taking nitric oxide donors, organic nitrites and nitrates, such as glyceryl trinitrate (nitroglycerin), sodium nitroprusside, amyl nitrite ("poppers")
- \* In men for whom sexual intercourse is inadvisable due to cardiovascular risk factors
- \* Severe hepatic impairment (decreased liver function)
- \* Severe impairment in renal function
- \* Hypotension (low blood pressure)
- \* Recent stroke or heart attack
- \* Hereditary degenerative retinal disorders (including genetic disorders of retinal phosphodiesterases)

### **Side effects**

Amongst sildenafil's serious adverse effects are: priapism, severe hypotension, myocardial infarction, ventricular arrhythmias, sudden death, stroke and increased intraocular pressure.

Common side effects include sneezing, headache, flushing, dyspepsia, prolonged erections, palpitations and photophobia. Visual changes including blurring of vision and a curious bluish tinge have also been reported.

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.

Some sildenafil users have complained of blurriness and loss of peripheral vision. In May of 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.

When used with an alpha blocker, take them at least four hours apart to avoid hypotension.

### **Other uses**

#### **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. Pfizer submitted an additional registration for sildenafil to the FDA, and sildenafil was approved for this indication in June 2005. The preparation is named Revatio, to avoid confusion with Viagra, and the 20 milligram tablets are white and round. Sildenafil joins bosentan and prostacyclin-based therapies for this condition.

### **Raynaud's phenomenon**

In 2005, Dr. Roland Fries and colleagues reported that sildenafil cut the frequency of Raynaud's phenomenon attacks, reduced their duration by roughly one half, and more than quadrupled the mean capillary blood velocity. This was a double-blind, placebo-controlled crossover trial and the patients had both the primary and secondary forms and had all discontinued the more conventional treatments for this.

### **Non-medical use**

#### **Aphrodisiac**

Sildenafil is commonly and increasingly used as an aphrodisiac. While there is no clinical evidence that it has aphrodisiac activity, many seem to believe it will improve sexual performance as well as erectile function and enhance the sexual experience that will occur.

#### **Recreational use**

Viagra's popularity with young adults has increased over the years. It is sometimes used recreationally. Some users mix Viagra with methylenedioxymethamphetamine (MDMA, ecstasy) in an attempt to compensate for the side effect common to many amphetamines of erectile dysfunction, a combination known as "sextasy", "rockin' and rollin'", or 'trail mix'."

#### **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.

#### **Chemical synthesis**

The preparation steps for synthesis of Viagra (sildenafil citrate) are as follows:

1. Methylation of 3-propylpyrazole-5-carboxylic acid ethyl ester with hot dimethyl sulfate.
2. Hydrolysis with aqueous NaOH to free acid.
3. Nitration with oleum/fuming nitric acid.
4. Carboxamide formation with refluxing thionyl chloride/NH<sub>4</sub>OH.
5. Reduction of nitro group to amino.
6. Acylation with 2-ethoxybenzoyl chloride.
7. Cyclization.
8. Sulfonation to the chlorosulfonyl derivative.
9. Condensation with 1-methylpiperazine.