*enoa repens* (*Sabal serrulata*). It contains not less than 11.0% of total fatty acids, calculated with reference to the dried drug. Protect from light.

**USP 31** (Saw Palmetto). The partially dried, ripe fruit of *Serenoa repens* (Arecaceae). Store in airtight containers. Protect from light.

### Profile

Saw palmetto is the dried fruit of the American dwarf palm tree, *Serenoa repens* (Arecaceae). It contains various steroidal compounds with anti-androgenic and oestrogenic activities, one of which is sitosterol (p.1373). Saw palmetto is used for the treatment of benign prostatic hyperplasia. Preparations of alcoholic or lipophilic extracts have typically been given in oral doses of 160 mg twice daily, or 320 mg once daily.

**Adverse effects.** ***EFFECTS ON THE LIVER.*** Cholestatic hepatitis occurred in a man who took a herbal preparation containing saw palmetto for 2 weeks to treat nocturia and hesitancy.[1]

1. Hamid S, *et al.* Protracted cholestatic hepatitis after the use of Prostata. *Ann Intern Med* 1997; **127:** 169–70.

**Uses.** ***BENIGN PROSTATIC HYPERPLASIA.*** A lipid hexane extract of saw palmetto has been shown to be generally superior to placebo,[1,2] and of similar efficacy to finasteride[3] in the treatment of benign prostatic hyperplasia (p.2178). A systematic review of randomised studies of various saw palmetto extracts concluded that they improve urological symptoms and flow measures.[4] However, a more recent double-blind study[5] concluded that treatment for one year was not superior to placebo for improving urinary symptoms and objective measures.

1. Champault G, *et al.* A double-blind trial of an extract of the plant Serenoa repens in benign prostatic hyperplasia. *Br J Clin Pharmacol* 1984; **18:** 461.
2. Plosker GL, Brogden RN. Serenoa repens (Permixon): a review of its pharmacology and therapeutic efficacy in benign prostatic hyperplasia. *Drugs Aging* 1996; **9:** 379–95.
3. Carraro J-C, *et al.* Comparison of phytotherapy (Permixon) with finasteride in the treatment of benign prostate hyperplasia: a randomized international study of 1,098 patients. *Prostate* 1996; **29:** 231–40.
4. Wilt T, *et al.* Serenoa repens for benign prostatic hyperplasia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 29/11/05).
5. Bent S, *et al.* Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; **354:** 557–66.

### Preparations

***USP 31:*** Saw Palmetto Capsules.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Beltrax Uno; Herbaccion Prostatico†; Permicaps; Permixon; Sereprostat†; ***Austral.:*** Bioglan Pro-Guard; Prosta†; ***Austria:*** Permixon; Prosta-Urgenin; ***Belg.:*** Prosta-Urgenin; Prostaserene; ***Braz.:*** Permixon†; Prostalium†; Prostat; Prostatal; Renopen; ***Chile:*** Prostafort; ***Cz.:*** Capistan; Prosta-Urgenin; Prostakan Mono; Prostamol Uno; Spalda Sabal; ***Fr.:*** Permixon; ***Ger.:*** Azuprostat Sabal†; Eviprostat-S; Hyperprost Uno; Normurol†; Planturol†; Prosta Urgenin Uno; Prostagutt mono; Prostagutt uno; Prostaplant†; Prostess; Remiprostan uno; Sabacur uno; Sabal; Sabal uno; Sabalvit; Sabonal Uno†; Sita; Steiprostat; Strogen; Talso; ***Gr.:*** Libeprosta; Urisedon†; ***Hung.:*** Prostakan†; Prostamol Uno; Saballo; Strogen Uno; ***Indon.:*** Lanaprost; Prostakur; ***Israel:*** Permixon; ***Ital.:*** Biosern†; Permixon; Prosteren; Rilaprost; Saba; Serpens; ***Mex.:*** Permixon; Prostasan; Prostex; Urogutt; ***Pol.:*** Bioprost; Fitoprost; Permixon; Prostamol Uno; Prostaplant; Sterko; ***Port.:*** Permixon; Prostiva†; Sereprosta; ***Rus.:*** Permixon (Пермиксон); Prostamol Uno (Простамол Уно); Prostaplant (Простаплант); ***Singapore:*** Permixon; ***Spain:*** Permixon; Sereprostat; ***Switz.:*** Permixon; Prosta-Urgenine; ProstaMed; Prostasan; SabCaps; ***Thai.:*** Permixon; Urogutt; ***UK:*** Prostasan; Sabalin; ***Venez.:*** Permixon†.

**Multi-ingredient:** ***Arg.:*** Anastim con RTH; Argeal; Catiz Plus; Keracnyl; Normoprost Plus; PR21; Sabal; Ultracal; ***Austral.:*** Bioglan Mens Super Soy/Clover; Extralife Flow-Care; Lifechange Mens Complex with Saw Palmetto†; Serenoa Complex†; Urapro†; Urgenin†; Urinase†; ***Austria:*** Prostagutt; Spasmo-Urgenin; Urgenin; ***Belg.:*** Urgenin; ***Canad.:*** Damiana-Sarsaparilla Formula†; Prostate Ease; Prostease; ProstGard†; ***Cz.:*** Prostakan Forte; ***Fr.:*** Argeal; Kelual DS; Keracnyl; Sabal; ***Ger.:*** Cefasabal; Granu Fink Prosta; Nephroselect M; Prostagutt forte; ***Hong Kong:*** Palmetto Plus†; Phyto-Ease; Prostease; Sawmetto Vivo-Livo†; Urgenin; ***Indon.:*** Instink; Maxirex; Menolia; Reximax; Soprost; ***Israel:*** Urgenin; ***Ital.:*** Biothymus M Urto; Pluvio; Prostaplant; ***Malaysia:*** Prostakan†; Total Man†; ***Mex.:*** Prosgutt; ***Pol.:*** Naturapia Prostata; Penigra; ***Port.:*** Efluvium Anti-caspa; Efluvium Anti-seborreico; Neo Urgenin; Spasmo-Urgenin†; ***Rus.:*** Prostagutt Forte (Простагут Форте); ***S.Afr.:*** Spasmo-Urgenin†; ***Singapore:*** Palmetto Plus; ***Spain:*** Neo Urgenin; Spasmo-Urgenin; Urgenin; ***Switz.:*** Granu Fink Prosta; Phytomed Prosta†; Prosta-Caps Chassot N; Prostagutt-F; ***Thai.:*** Spasmo-Urgenin; ***UK:*** Antiglan; Daily Fatigue Relief; Damiana and Kola Tablets; Elixir Damiana and Saw Palmetto; Regina Royal Concorde; Strength; ***Venez.:*** Sabal.

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## Sildenafil Citrate *(BANM, USAN, rINNM)*

Citrato de sildenafilo; Sildénafil, citrate de; Sildenafil Sitrat; Sildenafili citras; UK-92480-10. 5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1,6-dihydro-1-methyl-3-propylpyrazolo[4,3-*d*]pyrimidin-7-one citrate; 1-{[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl}-4-methylpiperazone citrate.

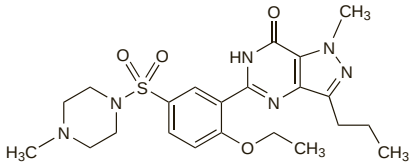
Сильденафила Цитрат

$C_{22}H_{30}N_6O_4S,C_6H_8O_7$ = 666.7.

*CAS — 139755-83-2 (sildenafil); 171599-83-0 (sildenafil citrate).*

*ATC — G04BE03.*

*ATC Vet — QG04BE03.*



*(sildenafil)*

**Stability.** Sildenafil citrate tablets were ground to a powder and combined with a 1:1 mixture of methylcellulose 1% and simple syrup (USNF), or with a 1:1 mixture of *Ora-Plus* and *Ora-Sweet* (both *Paddock, USA*), to a nominal concentration of 2.5 mg/mL sildenafil citrate in each suspension.[1] Both suspensions were found to be chemically and physically stable for 91 days in plastic bottles, at both 4° and 25°.

1. Nahata MC, *et al.* Extemporaneous sildenafil citrate oral suspensions for the treatment of pulmonary hypertension in children. *Am J Health-Syst Pharm* 2006; **63:** 254–7.

### Adverse Effects

Adverse effects most commonly reported with sildenafil are headache, flushing, and dyspepsia. Also common are visual disturbances such as blurred vision, photophobia, chromatopsia, cyanopsia, eye irritation, pain and redness of the eyes. Retinal haemorrhage has occurred, and non-arteritic anterior ischaemic optic neuropathy (NAION) causing permanent loss of vision has been reported rarely. Other common adverse effects include dizziness, insomnia, anxiety, vertigo, epistaxis, nasal congestion, pyrexia, and gastrointestinal disturbances such as diarrhoea and vomiting. Priapism can occur.

Other adverse effects include skin rashes, erythema, alopecia, limb and/or back pain, myalgia, facial oedema, fluid retention, paraesthesia, and urinary-tract infection. Dyspnoea, cough, rhinitis, sinusitis, bronchitis, and cellulitis can occur. Sudden decrease or loss of hearing has been reported. Other reported effects include anaemia, leucopenia, gynaecomastia, urinary frequency or incontinence, haematuria, and seizures.

Cerebrovascular haemorrhage and transient ischaemic attacks have occurred. There have also been reports of palpitations, syncope, hypertension, hypotension, and serious cardiovascular events including myocardial infarction, arrhythmias, tachycardia, unstable angina, and sudden cardiac death.

◊ Reviews.

1. Vitezic D. A risk-benefit assessment of sildenafil in the treatment of erectile dysfunction. *Drug Safety* 2001; **24:** 255–65.
2. Padma-nathan H, *et al.* A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; **60** (suppl 2): 67–90.

**Convulsions.** A report[1] of 2 patients who had a first tonic-clonic seizure shortly after taking sildenafil.

1. Gilad R, *et al.* Tonic-clonic seizures in patients taking sildenafil. *BMJ* 2002; **325:** 869.

**Effects on the cardiovascular system.** The effects of phosphodiesterase type-5 inhibitors (sildenafil, tadalafil, and vardenafil) on the cardiovascular system,[1,2] and the potential risks of sexual activity in men with cardiovascular disease,[3] have been reviewed.

There has been considerable uncertainty about the potential cardiovascular risk associated with sildenafil treatment. Minor effects associated with vasodilatation, such as headache and flushing are relatively common, but in patients without pre-existing cardiovascular risk factors the risk of serious cardiovascular events associated with the drug appears to be low. However, there have been reports of myocardial infarction in patients who had no apparent risk factors,[4,5] and a consensus document issued by the American College of Cardiology and the American Heart Association (ACC/AHA) has pointed out that patients with erectile dysfunction are mostly over 45 years of age and are more likely to have risk factors predisposing them to cardiovascular disease.[6]

As of November 1998, 130 deaths in US patients taking sildenafil had been reported to the FDA; 3 of these were due to stroke and 77 to some other cardiovascular event.[7] The nature of the relationship between drug and event was considered unclear, but some of these patients were also receiving nitrates, a combination now contra-indicated because of the greatly increased risk of potentially life-threatening hypotension.[6] The Australian Adverse Drug Reactions Advisory Committee[8] stated in June 2002 that it had received 773 reports of adverse reactions associated with the use of sildenafil. There were 20 reports of myocardial infarction, including 4 fatalities; 9 of these 20 patients had pre-existing cardiovascular disease or diabetes or were considered to be at high risk of cardiovascular disease, and 1 patient was taking nitrates. Other cardiovascular effects reported included 26 reports of chest pain and 10 other fatalities (6 sudden unexplained deaths, 2 strokes, and 2 subarachnoid haemorrhages). However, it was pointed out that the timing of these adverse effects in relation to sildenafil ingestion was often not reported and that, since sildenafil is taken in the context of sexual activity and, in some cases, underlying coronary disease, the contribution of sildenafil to cardiac events was difficult to assess.

It is still uncertain whether patients with **pre-existing** cardiovascular disease are at increased risk when taking sildenafil without concomitant nitrates. The ACC/AHA consensus statement noted that the evidence was scanty and suggested that sildenafil could be used, but with caution, in patients with stable *coronary artery disease* provided that nitrates were not taken.[6] A later review[9] and studies using exercise testing[10,11] also concluded that sildenafil appeared to be well tolerated in most patients with chronic stable coronary artery disease. In men with mild to moderate chronic *heart failure*, small studies have found that sildenafil was well tolerated and effective for erectile dysfunction,[12-14] and improved measures of exercise capacity.[12] Analyses[15,16] of combined trial data have examined the effects of sildenafil in men stabilised on antihypertensive treatment (including diuretics, beta blockers, alpha blockers, ACE inhibitors, and calcium-channel blockers) compared with men who did not have *hypertension*. Similar results were found for both groups in terms of sildenafil's efficacy for erectile dysfunction.[16] Also, changes in blood pressure and heart rate after a dose of sildenafil,[15] and the incidence of treatment-related adverse effects that were potentially related to blood pressure decrease,[16] were not significantly different between the groups. Evidence to assess the risk in other cardiovascular disorders is less extensive, although a case report of a patient with hypertrophic *cardiomyopathy* who had cardiovascular adverse effects after a dose of sildenafil suggested that the drug may precipitate an unstable haemodynamic state in this condition.[17]

1. Brindis RG, Kloner RA. Sildenafil in patients with cardiovascular disease. *Am J Cardiol* 2003; **92** (suppl): 26M–36M.
2. Kloner RA. Cardiovascular effects of the 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation* 2004; **110:** 3149–55.
3. Kostis JB, *et al.* Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). *Am J Cardiol* 2005; **96:** 313–21.
4. Feenstra J, *et al.* Acute myocardial infarction associated with sildenafil. *Lancet* 1998; **352:** 957–8.
5. Kekilli M, *et al.* Acute myocardial infarction after sildenafil citrate ingestion. *Ann Pharmacother* 2005; **39:** 1362–4.
6. Cheitlin MD, *et al.* Use of sildenafil (Viagra) in patients with cardiovascular disease. ACC/AHA Expert Consensus Document. *J Am Coll Cardiol* 1999; **33:** 273–82. Correction. *ibid.*; **34:** 1850. Also available at: http://circ.ahajournals.org/cgi/reprint/99/1/168.pdf (accessed 29/11/05)
7. FDA. Postmarketing safety of sildenafil citrate (Viagra): summary of reports of death in Viagra users received from marketing (late March) through mid-November 1998. Available at: http://www.fda.gov/cder/consumerinfo/viagra/safety3.htm (accessed 29/11/05)
8. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
9. Tran D, Howes LG. Cardiovascular safety of sildenafil. *Drug Safety* 2003; **26:** 453–60.
10. Arruda-Olson AM, *et al.* Cardiovascular effects of sildenafil during exercise in men with known or probable coronary artery disease: a randomized crossover trial. *JAMA* 2002; **287:** 719–25.
11. Fox KM, *et al.* Sildenafil citrate does not reduce exercise tolerance in men with erectile dysfunction and chronic stable angina. *Eur Heart J* 2003; **24:** 2206–12.
12. Bocchi EA, *et al.* Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction. *Circulation* 2002; **106:** 1097–1103.
13. Webster LJ, *et al.* Use of sildenafil for safe improvement of erectile function and quality of life in men with New York Heart Association classes II and III congestive heart failure: a prospective, placebo-controlled, double-blind crossover trial. *Arch Intern Med* 2004; **164:** 514–20.
14. Katz SD, *et al.* Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; **95:** 36–42.
15. Zusman RM, *et al.* Effect of sildenafil citrate on blood pressure and heart rate in men with erectile dysfunction taking concomitant antihypertensive medication. *J Hypertens* 2000; **18:** 1865–9.
16. Kloner RA, *et al.* Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens* 2001; **14:** 70–3.
17. Stauffer J-C, *et al.* Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999; **341:** 700–701.

**Effects on the ears.** As of October 2007, the US FDA had received a total of 29 postmarketing reports of sudden hearing loss with phosphodiesterase type-5 inhibitors. The problem was sometimes accompanied by tinnitus, vertigo, or dizziness. In most of the cases, the hearing loss involved one ear, and it was

either a partial or complete loss of hearing. In about one-third of cases, the loss was temporary. While a causal relationship could not be established, patients should be advised that hearing loss may be related to these drugs, and to seek medical attention if affected.[1]

1. FDA. FDA announces revisions to labels for Cialis, Levitra and Viagra: potential risk of sudden hearing loss with ED drugs to be displayed more prominently (issued 18th October 2007). Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html (accessed 18/01/08)

**Effects on the eyes.** The Australian Adverse Drug Reactions Advisory Committee[1] stated in June 2002 that it had received 65 reports of abnormal vision from a total of 773 adverse reactions associated with use of sildenafil reported over 3 years. A bluish tinge or haze to vision and some increased light sensitivity has been reported by patients taking sildenafil, with the percentage of reports increasing with increasing dose.[2] The visual symptoms usually peak 1 to 2 hours after ingestion and resolve about 3 to 4 hours later. The effects of a single dose of sildenafil 100 mg were studied in 5 healthy subjects.[3] Electroretinogram measurements showed significant changes that correlated well with plasma-sildenafil concentrations, peaking at 1 hour after administration and showing complete recovery at the 6-hour measurements. Inhibition of phosphodiesterase type-6 in rod photoreceptors is the most likely mechanism of sildenafil-associated retinal dysfunction. However, there is as yet no clear evidence of retinal toxic effects or whether repeated dosing with sildenafil causes prolonged or further retinal dysfunction.[2,3] Likewise, it remains to be determined whether recovery of function as plasma-sildenafil concentrations subside also occurs in older patients or those with retinal degenerative disorders such as retinitis pigmentosa.

Other visual disturbances reported in patients taking sildenafil have included temporary loss of vision and increased intra-ocular pressure.[4] A 69-year-old man who had permanent loss of vision in one eye a few hours after taking sildenafil 100 mg was found to have an occlusion in a retinal artery.[5] In another similar case of retinal artery occlusion[6] the patient also had uncontrolled hypertension; the authors suggested that embolisation by a pre-existing arteriosclerotic plaque of the carotid artery resulted from elevated blood pressure and cardiac workload during sexual activity, rather than as a direct adverse effect of sildenafil.

Several cases of persistent blurred vision and visual loss caused by nonarteritic anterior ischaemic optic neuropathy (NAION; vascular insufficiency and ischaemia at the optic nerve head) associated with sildenafil use have been reported.[7-10] Generally, visual defects developed in one eye only within 24 hours of sildenafil ingestion, although many of these men had taken doses of sildenafil on past occasions without adverse effect. A small number of cases have also been reported for tadalafil[10-13] and vardenafil.[10] However, many of these men had underlying anatomic or vascular risk factors for NAION, including low cup to disc ratio (crowded disc), age over 50, diabetes, hypertension, ischaemic heart disease, hyperlipidaemia, and smoking. As of May 2005 the FDA had concluded that it was not possible to determine whether NAION was directly related to the use of phosphodiesterase type-5 inhibitors, the patients' underlying vascular risk factors or anatomical defects, a combination of these factors, or other factors.[10]

1. Adverse Drug Reactions Advisory Committee (ADRAC). Sildenafil—three years experience. *Aust Adverse Drug React Bull* 2002; **21:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0206.pdf (accessed 02/09/08)
2. Marmor MF. Sildenafil (Viagra) and ophthalmology. *Arch Ophthalmol* 1999; **117:** 518–19.
3. Vobig MA, *et al.* Retinal side-effects of sildenafil. *Lancet* 1999; **353:** 375.
4. Committee on Safety of Medicines/Medicines Control Agency. Sildenafil (Viagra). *Current Problems* 1999; **25:** 16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023713&RevisionSelectionMethod=LatestReleased (accessed 02/09/08)
5. Tripathi A, O'Donnell N. Branch retinal artery occlusion; another complication of sildenafil. *Br J Ophthalmol* 2000; **84:** 934–5.
6. Bertolucci A, *et al.* Hemi-retinal artery occlusion associated with sexual activity and sildenafil citrate (Viagra). *Acta Ophthalmol Scand* 2003; **81:** 198–200.
7. Boshier A, *et al.* A case of nonarteritic ischemic optic neuropathy (NAION) in a male patient taking sildenafil. *Int J Clin Pharmacol Ther* 2002; **40:** 422–3.
8. Pomeranz HD, *et al.* Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002; **109:** 584–7.
9. Pomeranz HD, Bhavsar AR. Nonarteritic ischemic optic neuropathy developing soon after use of sildenafil (Viagra): a report of seven new cases. *J Neuroophthalmol* 2005; **25:** 9–13.
10. FDA. Alert 07/2005: Sildenafil (marketed as Viagra). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/sildenafilHCP.pdf (accessed 28/07/05)
11. Peter NM, *et al.* Tadalafil-associated anterior ischaemic optic neuropathy. *Eye* 2005; **19:** 715–17.
12. Escaravage GK, *et al.* Tadalafil associated with anterior ischemic optic neuropathy. *Arch Ophthalmol* 2005; **123:** 399–400.
13. Bollinger K, Lee MS. Recurrent visual field defect and ischemic optic neuropathy associated with tadalafil rechallenge. *Arch Ophthalmol* 2005; **123:** 400–401.

**Effects on mental function.** There have been a few cases reported[1-3] of transient global amnesia after the use of sildenafil or tadalafil. Between January 1998 and February 2001, the FDA had received 35 reports of amnesia in which sildenafil was listed as the primary causal suspect.[4]

1. Gandolfo C, *et al.* Sildenafil and transient global amnesia. *Neurol Sci* 2003; **24:** 145–6.
2. Savitz SA, Caplan LR. Transient global amnesia after sildenafil (Viagra) use. *Neurology* 2002; **59:** 778.
3. Schiefer J, Sparing R. Transient global amnesia after intake of tadalafil, a PDE-5 inhibitor: a possible association? *Int J Impot Res* 2005; **17:** 383–4.
4. Milman HA, Arnold SB. Neurologic, psychological, and aggressive disturbances with sildenafil. *Ann Pharmacother* 2002; **36:** 1129–34.

## Precautions

Caution is required in patients with hepatic or severe renal impairment, and dosage reduction of sildenafil may be necessary. Care is also needed in patients with anatomical deformation of the penis or haematological disorders that may predispose them to priapism. In the event of prolonged erection (for more than 4 hours), patients should seek medical assistance, as penile tissue damage and permanent loss of potency can occur. Patients are also advised to stop taking sildenafil and seek medical advice in cases of sudden visual or hearing loss. Sildenafil should not be given to those with loss of vision in one eye caused by non-arteritic anterior ischaemic optic neuropathy (NAION), regardless of whether this was in connection with previous phosphodiesterase type-5 inhibitors or not. Patients who experience dizziness or visual disturbances should not drive or operate hazardous machinery.

The safety of sildenafil is uncertain in patients with severe hepatic impairment, bleeding disorders, active peptic ulceration, hypotension, hypertension, a recent history of stroke, myocardial infarction, or life-threatening arrhythmia, unstable angina, heart failure, or retinal disorders such as retinitis pigmentosa (a minority of whom have genetic disorders of retinal phosphodiesterases). Licensed product information advises that it should not be used in these groups.

**Cardiovascular disease.** For mention of a consensus statement on the use of sildenafil in patients with cardiovascular disease, see above.

## Interactions

Sildenafil or other phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. Sildenafil may also enhance the hypotensive effect of nicorandil and use of the two drugs together should be avoided. Symptomatic hypotension may also occur when phosphodiesterase type-5 inhibitors are given with alpha blockers. Generally, the patient should be stabilised on alpha blocker therapy before the phosphodiesterase type-5 inhibitor is started at a low dose and adjusted according to response. Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4, such as cimetidine, delavirdine, erythromycin, itraconazole, and ketoconazole, may reduce the clearance of phosphodiesterase type-5 inhibitors, necessitating a reduction in dosage. Plasma concentrations of phosphodiesterase type-5 inhibitors are significantly increased by HIV-protease inhibitors, and particularly so by ritonavir-boosted regimens. Such combinations should not be given unless absolutely essential. Grapefruit juice should be avoided with sildenafil or other phosphodiesterase type-5 inhibitors as it may increase their plasma concentrations. Inducers of CYP3A4, such as rifampicin, are likely to decrease plasma concentrations of phosphodiesterase type-5 inhibitors. Bosentan also reduces exposure to sildenafil.

Specific dosage recommendations have been made for the use of phosphodiesterase type-5 inhibitors with many of these drugs; see Uses and Administration under Sildenafil (below), Tadalafil (p.2196), and Vardenafil (p.2199).

**Antivirals.** Rises in sildenafil concentrations after use of *saquinavir* or *ritonavir* were consistent[1] with inhibition of metabolism mediated by the cytochrome P450 isoenzyme CYP3A4. The larger increases seen with ritonavir may be due to its additional inhibition of the isoenzyme CYP2C9. Fatal myocardial infarction has been reported[2] in a 47-year-old patient who took sildenafil 25 mg with ritonavir and saquinavir. In a study[3] of 6 HIV-positive men being treated with triple antiretroviral therapy that included *indinavir*, plasma concentrations of sildenafil were found to be significantly increased compared with historical controls.

1. Muirhead GJ, *et al.* Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Pharmacol* 2000; **50:** 99–107.
2. Hall MCS, Ahmad S. Interaction between sildenafil and HIV-1 combination therapy. *Lancet* 1999; **353:** 2071–2.
3. Merry C, *et al.* Interaction of sildenafil and indinavir when co-administered to HIV-positive patients. *AIDS* 1999; **13:** F101–F107.

**Cardiovascular drugs.** For the effects of sildenafil in men stabilised on *antihypertensives* in general, see Effects on the Cardiovascular System, above. For mention of a possible interaction between sildenafil and *verapamil*, see Immunosuppressants, below.

The plasma concentration of sildenafil was reduced by *bosentan* in a study[1] of 10 patients with pulmonary hypertension, probably by induction of the cytochrome P450 isoenzyme CYP3A4, which would increase the metabolism of sildenafil. The use of bosentan with sildenafil in pulmonary hypertension has been reported (see below) and this potential interaction should be taken into account.

1. Paul GA, *et al.* Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* 2005; **60:** 107–12.

**Dihydrocodeine.** The use of dihydrocodeine with sildenafil was associated with priapism in 2 men who had previously been treated successfully with sildenafil.[1] The first patient had two prolonged erections, lasting 4 and 5 hours, and the effect did not recur when the dihydrocodeine was stopped. The second patient had priapism on 3 occasions in the first week of dihydrocodeine treatment, but not in the subsequent 2 weeks despite continuing both drugs.

1. Goldmeier D, Lamba H. Prolonged erections produced by dihydrocodeine and sildenafil. *BMJ* 2002; **324:** 1555.

**Food.** *Grapefruit juice* has been shown to increase bioavailability but delay absorption of sildenafil in healthy subjects.[1]

1. Jetter A, *et al.* Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther* 2002; **71:** 21–9.

**Immunosuppressants.** Studies in men with erectile dysfunction who were receiving *tacrolimus* after kidney transplantation found that sildenafil had no effect on tacrolimus pharmacokinetics.[1,2] However, the pharmacokinetic profile of sildenafil differed from that reported in healthy subjects; the maximal plasma concentration was higher, the area under the concentration-time curve was increased, and the elimination half-life was prolonged.[1] Reductions in blood pressure were also found when sildenafil was given, although this may have been due to an interaction with *verapamil*. The authors suggested that an initial dose of 25 mg sildenafil should be used, and that on the days of sildenafil use the doses of antihypertensive drugs may need to be adjusted according to blood pressure response.[1,2]

1. Christ B, *et al.* Interactions of sildenafil and tacrolimus in men with erectile dysfunction after kidney transplantation. *Urology* 2001; **58:** 589–93.
2. Christ B, *et al.* Investigation on interaction between tacrolimus and sildenafil in kidney-transplanted patients with erectile dysfunction. *Int J Clin Pharmacol Ther* 2004; **42:** 149–56.

**Nitrates.** Giving sildenafil 50 mg to patients receiving *isosorbide mononitrate*, or sublingual *glyceryl trinitrate* given 1 hour after sildenafil, resulted in substantially greater decreases in blood pressure than when the nitrate was given alone in 2 cross-over studies in patients with angina.[1] Treatment-related adverse effects were reported in 8 of 16 patients who received sildenafil with isosorbide mononitrate and 3 of 15 who took sildenafil with glyceryl trinitrate. The authors confirmed that sildenafil should not be taken with nitrates.

1. Webb DJ, *et al.* Sildenafil citrate potentiates the hypotensive effects of nitric oxide donor drugs in male patients with stable angina. *J Am Coll Cardiol* 2000; **36:** 25–31.

## Pharmacokinetics

Sildenafil is rapidly absorbed after an oral dose, with a bioavailability of about 40%. Peak plasma concentrations are attained within 30 to 120 minutes; the rate of absorption is reduced when sildenafil is given with food.

Sildenafil is widely distributed into tissues and is about 96% bound to plasma proteins. It is metabolised in the liver mainly by cytochrome P450 isoenzymes CYP3A4 (the major route) and CYP2C9. The major metabolite, *N*-desmethylsildenafil (UK-103320) also has some activity. The terminal half-lives of sildenafil and the *N*-desmethyl metabolite are about 4 hours.

Sildenafil is excreted as metabolites, mainly in the faeces, and to a lesser extent the urine. Clearance may be reduced in the elderly and in patients with hepatic or severe renal impairment.

◊ References.


1. Nichols DJ, *et al.* Pharmacokinetics of sildenafil citrate after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 5S–12S.
2. Muirhead GJ, *et al.* The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br J Clin Pharmacol* 2002; **53** (suppl 1): 21S–30S.
3. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.


## Uses and Administration

Sildenafil is a phosphodiesterase type-5 inhibitor used in the management of erectile dysfunction and pulmonary arterial hypertension. It is given orally as the citrate although doses are expressed in terms of the base; 14 mg of sildenafil citrate is equivalent to about 10 mg of sildenafil.

In **erectile dysfunction** the usual dose is equivalent to sildenafil 50 mg about one hour before sexual intercourse. The dose may be increased or decreased depending on response. The maximum recommended dose is 100 mg, and sildenafil should not be taken more than once in 24 hours.

- An initial dose of 25 mg has been suggested in the USA for patients over 65 years of age, though such initial reductions are not considered necessary in the UK.
- An initial dose of no more than 25 mg daily is advised in patients taking sildenafil with inhibitors of cytochrome P450 isoenzyme CYP3A4; the dose should not exceed 25 mg every 48 hours if given with ritonavir-boosted HIV-protease inhibitors, although such a combination is best avoided entirely (see Interactions, above).
- In patients stabilised on alpha blocker therapy, an initial dose of sildenafil 25 mg should be considered.

To improve exercise ability in **pulmonary arterial hypertension**, sildenafil is given orally in a dose of 20 mg three times daily. The dose may need adjustment to account for drug interactions (see above) although licensed product information suggests that in these patients no adjustment is required when sildenafil is given with erythromycin or saquinavir. It also suggests that no adjustment is generally needed for pulmonary hypertension patients with renal or hepatic impairment, although patients with severe hepatic impairment (Child-Pugh category C) have not been studied. Although not licensed in the UK for children, the *BNFC* allows for a dose in neonates and children up to 18 years of age, of 250 to 500 micrograms/kg given orally every 4 to 8 hours, adjusted according to response up to a maximum of 2 mg/kg every 4 hours. Treatment should be withdrawn gradually in neonates.

For doses in hepatic and renal impairment, see below.

**Administration in hepatic impairment.** Sildenafil clearance is reduced in patients with hepatic impairment. Safety has not been established in patients with severe hepatic impairment (Child-Pugh class C) and its use is contra-indicated in these patients for this reason.

Licensed product information for patients with **erectile dysfunction** recommends an initial dose of 25 mg in patients with hepatic impairment.

Licensed product information for patients with **pulmonary arterial hypertension** states that initial dose adjustments are not needed for patients with mild or moderate hepatic impairment (Child-Pugh class A or B); in the UK, it is recommended that a reduction to 20 mg twice daily should be considered if therapy is not well tolerated.

**Administration in renal impairment.** Sildenafil clearance is reduced in patients with severe renal impairment.

Licensed product information for patients with **erectile dysfunction** recommends that in these patients, an initial dose of 25 mg should be considered. In the UK it is stated that the dose may be increased to 50 or 100 mg, if needed and tolerated.

Licensed product information for patients with **pulmonary arterial hypertension** states that no dose adjustments are required for patients with renal impairment, including those with severe renal impairment (creatinine clearance less than 30 mL/minute). However, in the UK, consideration of a reduction to 20 mg twice daily is suggested if therapy is not well tolerated.

**Erectile dysfunction.** Sildenafil, an inhibitor of phosphodiesterase type-5, is used as an oral therapy for erectile dysfunction (p.2179). It is effective in erectile dysfunction of psychogenic causes and organic causes such as diabetes mellitus, spinal-cord injury, and prostatectomy.

References.


1. Langtry HD, Markham A. Sildenafil: a review of its use in erectile dysfunction. *Drugs* 1999; **57:** 967–89.
2. Montorsi F, *et al.* Efficacy and safety of fixed-dose oral sildenafil in the treatment of erectile dysfunction of various etiologies. *Urology* 1999; **53:** 1011–18.
3. Rendell MS, *et al.* Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. *JAMA* 1999; **281:** 421–6.
4. Kedia S, *et al.* Treatment of erectile dysfunction with sildenafil citrate (Viagra) after radiation therapy for prostate cancer. *Urology* 1999; **54:** 308–12.
5. Zippe CD, *et al.* Role of Viagra after radical prostatectomy. *Urology* 2000; **55:** 241–5.
6. Fink HA, *et al.* Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2002; **162:** 1349–60.
7. Fedele D, *et al.* Experience with sildenafil in diabetes. *Diabetes Nutr Metab* 2002; **15:** 49–52.
8. Derry F, *et al.* Efficacy and safety of sildenafil citrate (Viagra ) in men with erectile dysfunction and spinal cord injury: a review. *Urology* 2002; **60** (suppl): 49–57.
9. Raina R, *et al.* Long-term effect of sildenafil citrate on erectile dysfunction after radical prostatectomy: 3-year follow-up. *Urology* 2003; **62:** 110–15.
10. Carson CC. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. *Curr Urol Rep* 2003; **4:** 488–96.
11. Setter SM, *et al.* Phosphodiesterase 5 inhibitors for erectile dysfunction. *Ann Pharmacother* 2005; **39:** 1286–95.
12. Shields KM, Hrometz SL. Use of sildenafil for female sexual dysfunction. *Ann Pharmacother* 2006; **40:** 931–4.


**High-altitude disorders.** Hypoxic pulmonary hypertension associated with high altitude (p.1168) may respond to sildenafil. Small studies have shown some promising results.[1-3]


1. Ghofrani HA, *et al.* Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: a randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 2004; **141:** 169–77.
2. Richalet JP, *et al.* Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; **171:** 275–81.
3. Ricart A, *et al.* Effects of sildenafil on the human response to acute hypoxia and exercise. *High Alt Med Biol* 2005; **6:** 43–9.


**Oesophageal motility disorders.** Preliminary studies[1-3] have investigated the use of sildenafil in patients with oesophageal motility disorders (p.1702) such as achalasia or nutcracker oesophagus. Although some benefit has been reported, further studies are needed.


1. Bortolotti M, *et al.* Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. *Gastroenterology* 2000; **118:** 253–7.
2. Eherer AJ, *et al.* Effect of sildenafil on oesophageal motor function in healthy subjects and patients with oesophageal motor disorders. *Gut* 2002; **50:** 758–64.
3. Lee JI, *et al.* The effect of sildenafil on oesophageal motor function in healthy subjects and patients with nutcracker oesophagus. *Neurogastroenterol Motil* 2003; **15:** 617–23.


**Premature ejaculation.** Early reports have suggested that sildenafil may be effective in the management of premature ejaculation (p.2181) and the rationale for such use has been reviewed.[1]


1. Abdel-Hamid IA. Phosphodiesterase 5 inhibitors in rapid ejaculation: potential use and possible mechanisms of action. *Drugs* 2004; **64:** 13–26.


**Priapism.** Sildenafil has been reported to be effective in the treatment of priapism in 3 patients with sickle-cell disease.[1] In 2 of these patients, sildenafil was also successful in preventing further episodes of priapism when it was taken at the onset of symptoms.


1. Bialecki ES. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med* 2002; **113:** 252.


**Pulmonary hypertension.** Oral sildenafil has produced beneficial responses in patients with pulmonary arterial hypertension (p.1179) and may have a role, particularly in patients who fail to respond to other therapies. It has been given either alone[1-7] or with other treatments such as inhaled nitric oxide,[6] inhaled iloprost,[1] intravenous epoprostenol,[8,9] or oral beraprost.[10] Sildenafil has also been added to bosentan therapy, with some benefit, in a small number of patients.[11] For a report on the pharmacokinetic interaction of these 2 drugs see Cardiovascular Drugs, above. The results of short-term and long-term studies of sildenafil have been reviewed.[12,13] In a study[14] using single doses of phosphodiesterase type-5 inhibitors, it was found that sildenafil and tadalafil had greater selectivity for the pulmonary circulation than vardenafil, and that arterial oxygenation was improved by sildenafil only. In a pivotal study,[7] sildenafil improved exercise capacity and haemodynamics in patients. Sildenafil was given at 20, 40, or 80 mg orally three times daily. While there was no evidence of a dose-response relationship in the primary end-point of exercise capacity, there was a linear trend in the response in haemodynamic measures. In an extension study, all patients were treated with 80 mg orally three times daily if tolerated. Some have questioned whether the licensed dose of 20 mg three times daily is sufficient,[15] especially if patients are given bosentan at the same time, leading the authors of the original study to suggest that this may be used as an initial dose, with an increase to 40 or 80 mg three times daily in order to achieve or maintain favourable effects.[16]

Sildenafil has also been studied for paediatric pulmonary hypertension. Some consider that it may have a role in persistent pulmonary hypertension in neonates,[17,18] as well as in those with pulmonary arterial hypertension associated with congenital heart disease, or secondary to lung disease, or in postoperative pulmonary hypertension and in neonates who are difficult to wean from inhaled nitric oxide.[18] However, further controlled studies are needed.[17,18] Nevertheless, although unlicensed in the UK, the *BNFC* suggests that sildenafil may be given orally to neonates and children for pulmonary hypertension after cardiac surgery, weaning from nitric oxide, idiopathic pulmonary arterial hypertension, and persistent pulmonary hypertension of the newborn (see above for details of doses).

Sildenafil has also been reported to be of benefit in high-altitude pulmonary hypertension.[19]


1. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
2. Ghofrani HA, *et al.* Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet* 2002; **360:** 895–900.
3. Watanabe H, *et al.* Sildenafil for primary and secondary pulmonary hypertension. *Clin Pharmacol Ther* 2002; **71:** 398–402.
4. Carroll WD, Dhillon R. Sildenafil as a treatment for pulmonary hypertension. *Arch Dis Child* 2003; **88:** 827–8.
5. Sastry BKS, *et al.* Clinical efficacy of sildenafil in primary pulmonary hypertension: a randomized, placebo-controlled, double-blind, crossover study. *J Am Coll Cardiol* 2004; **43:** 1149–53.
6. Michelakis E, *et al.* Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. *Circulation* 2002; **105:** 2398–2403.
7. Galiè N, *et al.* Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; **353:** 2148–57.
8. Bhatia S, *et al.* Immediate and long-term hemodynamic and clinical effects of sildenafil in patients with pulmonary arterial hypertension receiving vasodilator therapy. *Mayo Clin Proc* 2003; **78:** 1207–13.
9. Stiebellehner L, *et al.* Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003; **123:** 1293–5.
10. Ikeda D, *et al.* Addition of oral sildenafil to beraprost is a safe and effective therapeutic option for patients with pulmonary hypertension. *J Cardiovasc Pharmacol* 2005; **45:** 286–9.
11. Hoeper MM, *et al.* Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; **24:** 1007–10.
12. Lee AJ, *et al.* Sildenafil for pulmonary hypertension. *Ann Pharmacother* 2005; **39:** 869–84.
13. Croom KF, Curran, MP. Sildenafil: a review of its use in pulmonary arterial hypertension. *Drugs* 2008; **68:** 383–97.
14. Ghofrani HA, *et al.* Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. *J Am Coll Cardiol* 2004; **44:** 1488–96.
15. Hoeper MM, Welte T. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1091.
16. Galiè N, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2006; **354:** 1092–3.
17. Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 18/01/08).
18. Leibovitch L, *et al.* Therapeutic applications of sildenafil citrate in the management of paediatric pulmonary hypertension. *Drugs* 2007; **67:** 57–73.
19. Aldashev AA, *et al.* Phosphodiesterase type 5 and high altitude pulmonary hypertension. *Thorax* 2005; **60:** 683–7.


**Raynaud's syndrome.** Sildenafil has been reported to be of benefit in Raynaud's phenomenon (see Vasospastic Arterial Disorders, p.1188) resistant to vasodilator therapy.[1]


1. Fries R, *et al.* Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112:** 2980–5.


## Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Anaus; Bifort; Erectol; Expit; Falic; File; Firmel; Incresil; Juvigor; Lorbinafil; Lumix; Magnus; Maxdosa; Maximo; Nexofil; Nitro; Openvas; Permitil; Segurex; Sildefil; Tecnomax; Viagra; Vigor Plus; Vimax; Virilon; Viripotens; Vorst; ***Austral.:*** Revatio; Viagra; ***Austria:*** Viagra; ***Belg.:*** Viagra; ***Braz.:*** Revatio; Viagra; ***Canad.:*** Viagra; ***Chile:*** Alfin; Dirtop; Erosfil; Helpin; Lifter; Novalif; Ripol; Seler; Siafil; Viagra; Vimax; Zilfic; ***Cz.:*** Revatio; Viagra; ***Denm.:*** Viagra; ***Fin.:*** Viagra; ***Fr.:*** Revatio; Viagra; ***Ger.:*** Viagra; ***Gr.:*** Viagra; ***Hong Kong:*** Viagra; ***Hung.:*** Revatio; Viagra; ***India:*** Caverta; Fiagra†; Juan; Penegra; Silagra; Viagra; ***Indon.:*** Viagra; ***Irl.:*** Viagra; ***Israel:*** Viagra; ***Ital.:*** Viagra; ***Jpn:*** Viagra; ***Malaysia:*** Viagra; ***Mex.:*** Apodefil; Viagra; ***Neth.:*** Revatio; Viagra; ***Norw.:*** Viagra; ***NZ:*** Revatio; Viagra; ***Philipp.:*** Andros; Viagra; ***Pol.:*** Viagra; ***Port.:*** Revatio; Viagra; ***Rus.:*** Viagra (Виагра); ***S.Afr.:*** Viagra; ***Singapore:*** Viagra; ***Spain:*** Viagra; ***Swed.:*** Revatio; Viagra; ***Switz.:*** Viagra; ***Thai.:*** Viagra; ***Turk.:*** Sildegra; Viagra; Vigrande; ***UK:*** Revatio; Viagra; ***USA:*** Revatio; Viagra; ***Venez.:*** Duroval; Itaka; Viagra; Viasek; Viasil; Vigrasol; Viosex; Viridil.

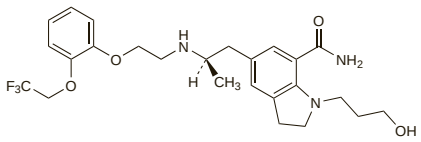
## Silodosin *(rINN)*

KMD-3213; Silodosina; Silodosine; Silodosinum. (−)-1-(3-Hydroxypropyl)-5-[(2*R*)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]-ethyl}amino)propyl]-2,3-dihydro-1*H*-indole-7-carboxamide.

Сильодозин

$C_{25}H_{32}F_3N_3O_4$ = 495.5.

*CAS — 160970-54-7.*



### Profile

Silodosin is an alpha$_1$-adrenoceptor blocker (p.1153) that is reported to be selective for the alpha$_{1A}$-adrenoceptor subtype. It is used orally in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Jpn:*** Urief.

## Solifenacin Succinate *(BANM, USAN, rINNM)*

Solifénacine, Succinate de; Solifenacini Succinas; Succinato de solifenacina; YM-905; YM-67905. (3*R*)-1-Azabicyclo[2.2.2]oct-3-yl (1*S*)-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate compound with butanedioic acid (1:1).

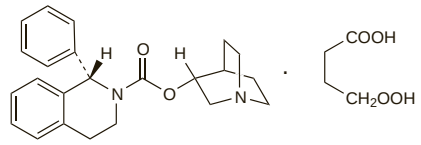
Солифенацина Суксинат

$C_{23}H_{26}N_2O_2,C_4H_6O_4$ = 480.6.

*CAS — 242478-37-1 (solifenacin); 242478-38-2 (solifenacin succinate).*

*ATC — G04BD08.*

*ATC Vet — QG04BD08.*



### Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Solifenacin succinate should be used with caution in patients also receiving inhibitors of the cytochrome P450 isoenzyme CYP3A4 (see Interactions and Uses and Administration, below). It should also be used with caution in hepatic and renal impairment.

### Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Exposure to solifenacin succinate may be increased by drugs that inhibit the cytochrome P450 isoenzyme CYP3A4. Although there is a lack of data, licensed product information also warns of the potential for interaction between solifenacin succinate and substrates or inducers of CYP3A4. Dosage adjustment for solifenacin succinate may be necessary (see Uses and Administration, below).

### Pharmacokinetics

After an oral dose, solifenacin succinate is absorbed from the gastrointestinal tract, with peak plasma concentrations reached after 3 to 8 hours and a bioavailability of about 90%. Solifenacin is about 98% bound to plasma proteins. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, and has a terminal half-life of 45 to 68 hours. Solifenacin is excreted mainly as metabolites in urine and faeces.

◊ References.


1. Kuipers ME, *et al.* Solifenacin demonstrates high absolute bioavailability in healthy men. *Drugs R D* 2004; **5:** 73–81.
2. Smulders RA, *et al.* Pharmacokinetics and safety of solifenacin succinate in healthy young men. *J Clin Pharmacol* 2004; **44:** 1023–33.


### Uses and Administration

Solifenacin succinate is a selective $M_3$ antimuscarinic with actions similar to those of atropine (p.1220). It is used in the treatment of urinary frequency, urgency, and incontinence in detrusor instability (p.2180). Usual doses of solifenacin succinate are 5 mg once daily by mouth, increased to 10 mg once daily if required. Maximum doses of 5 mg once daily are recommended in patients receiving drugs such as ketoconazole or ritonavir that are strong inhibitors of the cytochrome P450 isoenzyme CYP3A4. For doses in hepatic or renal impairment, see below.

◊ References.


1. Chapple CR, *et al.* Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; **93:** 303–10.
2. Cardozo L, *et al.* Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol (Baltimore)* 2004; **172:** 1919–24.
3. Haab F, *et al.* Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome. *Eur Urol* 2005; **47:** 376–84.
4. Chapple CR, *et al.* A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005; **48:** 464–70.
5. Abrams P, Swift S. Solifenacin is effective for the treatment of OAB dry patients: a pooled analysis. *Eur Urol* 2005; **48:** 483–7.
6. Payne CK. Solifenacin in overactive bladder syndrome. *Drugs* 2006; **66:** 175–90.


**Administration in hepatic and renal impairment.** Doses of 5 mg of solifenacin succinate once daily by mouth are recommended in patients with moderate hepatic impairment (Child-Pugh category B) or severe renal impairment (creatinine clearance less than 30 mL/minute). It should not be used in patients with severe hepatic impairment (Child-Pugh category C) or in those undergoing haemodialysis.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Vesicare; ***Austral.:*** Vesicare; ***Belg.:*** Vesicare; ***Cz.:*** Vesicare; ***Denm.:*** Vesicare; ***Fin.:*** Vesicare; ***Fr.:*** Vesicare; ***Ger.:*** Vesikur; ***Gr.:*** Vesicare; ***Hung.:*** Vesicare; ***Indon.:*** Vesicare; ***Irl.:*** Vesitirim; ***Ital.:*** Vesiker; ***Jpn:*** Vesicare; ***Neth.:*** Flomin; Uriclin; Vesicare; ***Norw.:*** Vesicare; ***NZ:*** Vesicare; ***Pol.:*** Vesicare; ***Port.:*** Flomin; Uriclin; Vesicare; ***Rus.:*** Vesicare (Везикар); ***S.Afr.:*** Vesicare; ***Spain:*** Vesicare; ***Swed.:*** Vesicare; ***UK:*** Vesicare; ***USA:*** Vesicare.

# Tadalafil *(BAN, USAN, rINN)*

GF-196960; IC-351; Tadalafili; Tadalafilo; Tadalafilum. (6*R*,12a*R*)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-[3,4-(methylenedioxy)-phenyl]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione.

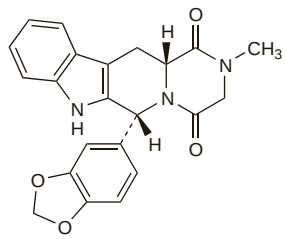
Тадалафил

$C_{22}H_{19}N_3O_4$ = 389.4.

*CAS — 171596-29-5.*

*ATC — G04BE08.*

*ATC Vet — QG04BE08.*



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of tadalafil:
Weekend Pill.

### Adverse Effects and Precautions

As for Sildenafil, p.2193. Visual disturbances may occur less frequently with tadalafil than with sildenafil. Dosage reductions may be required in patients with hepatic or renal impairment.

◊ References.


1. Montorsi F, *et al.* Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004; **45:** 339–44.


**Effects on the cardiovascular system.** References.


1. Kloner RA, *et al.* Cardiovascular effects of tadalafil. *Am J Cardiol* 2003; **92:** 37M–46M.


### Interactions

As for Sildenafil, p.2194.

**Antifungals.** Priapism occurred in a man who took two separate doses of tadalafil 10 mg, at least one month apart, during *itraconazole* treatment.[1] He was able to take sildenafil during itraconazole treatment without adverse effect. See also Uses and Administration, below, for recommended tadalafil dosage when it is taken with inhibitors of the cytochrome P450 isoenzyme CYP3A4.


1. Galatti L, *et al.* Interaction between tadalafil and itraconazole. *Ann Pharmacother* 2005; **39:** 200.


**Nitrates.** Phosphodiesterase type-5 inhibitors may potentiate the hypotensive effects of organic nitrates, and are therefore contra-indicated in patients receiving such drugs. An interaction between tadalafil and sublingual *glyceryl trinitrate* was reported to occur when glyceryl trinitrate was given within 24 hours after tadalafil but was no longer detectable at 48 hours.[1] Licensed product information recommends that if nitrate treatment is needed in a life-threatening situation then it should only be given at least 48 hours after the last dose of tadalafil and under close medical supervision.


1. Kloner RA, *et al.* Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; **42:** 1855–60.


### Pharmacokinetics

Tadalafil is well absorbed after an oral dose. Peak plasma concentrations are attained within 2 hours; the rate and extent of absorption are not affected by food.

Tadalafil is widely distributed into tissues and is about 94% bound to plasma proteins. It is metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolite, the methylcatechol glucuronide, is inactive. The mean half-life of tadalafil is about 17.5 hours.

Tadalafil is excreted, mainly as metabolites, in the faeces (61% of the dose), and to a lesser extent the urine (36% of the dose). Clearance may be reduced in the elderly and in patients with renal impairment.

◊ References.


1. Gupta M, *et al.* The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45:** 987–1003.
2. Forgue ST, *et al.* Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol* 2006; **61:** 280–8.
3. Forgue ST, *et al.* Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007; **63:** 24–35.


### Uses and Administration

Tadalafil is a phosphodiesterase type-5 inhibitor with actions and uses similar to those of sildenafil (p.2195). It is used in the management of erectile dysfunction (p.2179). Tadalafil is given orally in a usual dose of 10 mg at least 30 minutes before sexual intercourse and may be taken with or without food; the dose may be increased to 20 mg, or decreased to 5 mg, if necessary. Efficacy may persist for up to 36 hours after dosing. Tadalafil should not be taken more than once in 24 hours.

In the UK, for those who respond to tadalafil when taken as needed, and anticipate frequent use (defined as at least twice weekly), a regular daily regimen may be considered suitable. In these patients, the recommended dose is 5 mg once daily, taken at about the same time each day. The dose may be decreased to 2.5 mg once daily based on individual tolerability. In the USA, the recommended starting dose of tadalafil for daily use is 2.5 mg, taken at about the same time each day, which may then be increased to 5 mg, based on tolerability and efficacy. Dosage adjustments are not necessary in elderly patients; for recommendations in hepatic or renal impairment, see below.

Although the use of tadalafil with an alpha blocker is not recommended in the UK, the combination may be used in the USA; in patients stabilised on alpha blocker therapy a starting dose of tadalafil 5 mg may be used. In patients taking potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole or ritonavir-boosted HIV-protease inhibitors, the dose of tadalafil when used *as needed* should not exceed 10 mg once every 72 hours; when used on a *regular daily basis*, the dose should not exceed 2.5 mg.

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