due to hypersensitivity. In addition high parenteral doses can result in cardiac arrhythmias; intravenous or intramuscular doses should be given slowly. Thrombosis has been reported at the injection site.

Intracavernosal injection can cause dose-related priapism and local fibrosis has been reported after long-term therapy.

Papaverine should be given with caution to patients with reduced gastrointestinal motility. Caution is also advised in the presence of cardiac conduction disorders or unstable cardiovascular disease, especially when papaverine is given parenterally. Intravenous dosage is contra-indicated in patients with complete AV block.

Glaucoma. There appeared to be no basis for the manufacturers' recommendation that papaverine should be used with caution in patients with glaucoma.[1] There was no obvious mechanism to support such a warning and only 1 report of an adverse reaction had been received by the FDA. The author had given papaverine intracavernosally to patients with glaucoma and had observed no deterioration.

1. Swartz DA, Todd MW. Intracavernous papaverine and glaucoma. *JAMA* 1990; **264:** 570.

Intracavernosal administration. Systemic adverse effects occurring after intracavernosal injection of papaverine are infrequent but include dizziness and syncope,[1,2] probably related to the hypotensive effects of papaverine; abnormal liver function test results have also occurred.[1-3]

The most serious acute adverse effect is priapism[1,2,4] and patients should be instructed to seek medical help if an erection lasts for more than 4 hours. Detumescence can be effected by aspiration of blood from the corpus or by local injection of an alpha-adrenergic agonist such as adrenaline, metaraminol, or phenylephrine (see Priapism under Alprostadil, p.2184). Other local effects include haematoma, infection, and, on long-term therapy, fibrosis and penile distortion.[1,2]

Dispensing errors have resulted in inadvertent injection of *papaveretum* with potentially fatal consequences.[2,5,6]

1. Krane RJ, *et al.* Impotence. *N Engl J Med* 1989; **321:** 1648–59.
2. Bénard F, Lue TF. Self-administration in the pharmacological treatment of impotence. *Drugs* 1990; **39:** 394–8.
3. Levine SB, *et al.* Side effects of self-administration of intracavernous papaverine and phentolamine for the treatment of impotence. *J Urol (Baltimore)* 1989; **141:** 54–7.
4. Virag R. About pharmacologically induced prolonged erection. *Lancet* 1985; **i:** 519–20.
5. Robinson LQ, Stephenson TP. Self injection treatment for impotence. *BMJ* 1989; **299:** 1568.
6. Gregoire A. Self injection treatment for impotence. *BMJ* 1990; **300:** 537.

Interactions

Levodopa. For the effects of papaverine on levodopa, see p.808.

Pharmacokinetics

The biological half-life of papaverine given orally is reported to be between 1 and 2 hours, but there is wide interindividual variation. It is about 90% bound to plasma proteins.

Papaverine is mainly metabolised in the liver and excreted in the urine, almost entirely as glucuronide-conjugated phenolic metabolites.

The reports of infrequent systemic effects after intracavernosal injection of papaverine indicate that there is some distribution to the systemic circulation from the corpus cavernosus.

Uses and Administration

Papaverine is an alkaloid present in opium, although it is not related chemically or pharmacologically to the other opium alkaloids. Papaverine has a direct relaxant effect on smooth muscle which is attributed in part to its ability to inhibit phosphodiesterase. It has been given in the management of cerebral, peripheral, and coronary vascular disorders; it is also given as an antispasmodic for gastrointestinal disorders and coughs. However, there is little evidence to justify its clinical use in these conditions.

Papaverine hydrochloride has been given orally in doses of up to 600 mg daily. Sustained-release preparations have been used. The codecarboxylase derivative, cromesilate, hydrobromide, monophosadenine, nicotinate, sulfate, and teprosilate have also been used. Papaverine hydrochloride has also been given in doses of 30 to 120 mg by intramuscular or slow intravenous injection, repeated every 3 hours as needed (but see Adverse Effects and Precautions, above).

Papaverine hydrochloride has been given by injection into the corpus cavernosum of the penis for the treatment of erectile dysfunction (p.2179). Doses have ranged from 2.5 to 60 mg, but must be initially titrated by the prescriber. Doses up to about 30 mg have been combined with phentolamine.

Preparations

BP 2008: Papaverine Injection;
USP 31: Papaverine Hydrochloride Injection; Papaverine Hydrochloride Tablets.

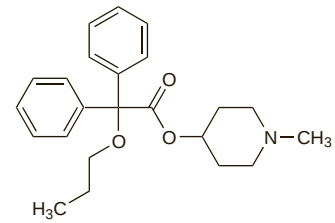
Proprietary Preparations (details are given in Part 3)
Arg.: Mesotina; Ova†; ***Braz.:*** Dipaverina†; ***USA:*** Pavabid†; ***Venez.:*** Atrophena†; Atroveran; Papaveryl; Tropaverin†.

Multi-ingredient: ***Arg.:*** Antipasmol; Antispasmina; Gastranil†; Hepatodirectol; Saltos†; Trixol†; ***Austria:*** Androskat; Asthma 23 D; Myocardon; Ora-Gallin compositum; ***Braz.:*** Analgosedan†; Calmazin†; Codeverin†; Dipirol†; Ductoveran; Espasmalgon†; Espasmocron; Gaba†; Melpaz†; Monotrean; Monotrean B6; Nicopaverina B6†; Nicopaverina†; Pasmalgin†; Plenocedan†; Revulsan†; Sedalene; Sedalin; Spasmotropin; Vagostesyl; ***Chile:*** Belupan†; Buton; Dipatropin; Dolospam; Papatropin†; ***Cz.:*** Contraspan†; Spasmoveralgin Neo†; ***Fr.:*** Acticarbine; ***Hong Kong:*** Bromhexine Compound; Codolax; Codomex Orange†; Codomex Purple†; Codoplex; Enterocin Compound; Methor-Co; Metoplex; ***Hung.:*** Bilagit†; Meristin; Neo-Bilagit; Troparinum; ***India:*** Brovon; ***Indon.:*** Sanmag; Spaslic; Spasmal; Spasminal; ***Israel:*** Patropin; Spasmalgin; ***Ital.:*** Antispasmina Colica; Monotrean†; ***Mex.:*** Acilin; Ayoral†; Taliviform†; ***Neth.:*** Androskat; ***Pol.:*** Biospasmil; Fortestomachicae; Spasticol; Tolargin; ***Port.:*** Antispasmina Colica; Cosmaxil†; ***Spain:*** Sulmetin Papaver; Sulmetin Papaverina†; ***Swed.:*** Spasmofen; ***Switz.:*** Dolopyrine†; Spasmosol; ***UK:*** Brovon; ***USA:*** Tri-Mix; ***Venez.:*** Atrobel; Cloverin†; Neo-Atropan†; Tropifen†.

Propiverine Hydrochloride *(BANM, rINNM)*

BUP-4 (propiverine); Hidrocloruro de propiverina; Propiverin Hidroklorür; Propivérine, Chlorhydrate de; Propiverini Hydrochloridum. 1-Methyl-4-piperidyl diphenylpropoxyacetate hydrochloride.

Пропиверина Гидрохлорид
$C_{23}H_{29}NO_3,HCl$ = 403.9.
CAS — 60569-19-9 (propiverine); 54556-98-8 (propiverine hydrochloride).
ATC — G04BD06.
ATC Vet — QG04BD06.



(propiverine)

Adverse Effects, Treatment, and Precautions

As for Atropine Sulfate, p.1219. Hypotension and drowsiness may also occur with propiverine. Propiverine is contra-indicated in patients with moderate or severe hepatic impairment (but see below). Liver enzyme values should be monitored in patients receiving long-term therapy. Skeletal retardation has occurred in the offspring of *animals* given high doses of propiverine during pregnancy and therefore its use is not recommended during pregnancy.

Interactions

As for antimuscarinics in general (see Atropine Sulfate, p.1220). Hypotension may occur in patients treated with propiverine and isoniazid. Drowsiness may be enhanced by drugs with CNS-depressant properties.

Pharmacokinetics

Propiverine is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved about 2.3 hours after oral doses. It undergoes extensive first-pass metabolism and the average absolute bioavailability is reported to be about 41%. Plasma concentrations of the principal metabolite, the *N*-oxide, greatly exceed those of the parent compound. Protein binding is about 90% for propiverine and 60% for the *N*-oxide metabolite. Propiverine and its metabolites are excreted in the urine, bile, and faeces. The elimination half-life is about 20 hours.

◊ References.

1. Haustein K-O, Hüller G. On the pharmacokinetics and metabolism of propiverine in man. *Eur J Drug Metab Pharmacokinet* 1988; **13:** 81–90.

Uses and Administration

Propiverine hydrochloride is a tertiary antimuscarinic with actions similar to those of atropine (p.1220). It is used for the management of urinary frequency, urgency, and incontinence (p.2180) in neurogenic bladder disorders and in idiopathic detrusor instability. Usual oral doses of propiverine hydrochloride are 15 mg two or three times daily, increased to 4 times daily if required. Some patients may respond to 15 mg once daily. A daily dose of 60 mg should not be exceeded. Propiverine hydrochloride can also be given as a modified-release preparation in a dose of 30 mg once daily.

Administration in hepatic impairment. Although UK licensed product information for propiverine does not recommend its use in patients with moderate or severe hepatic impairment some[1] suggest that on pharmacokinetic grounds it may be given to those with mild to moderate degrees of impairment at recommended doses without increasing the risk of adverse effects.

1. Siepmann M, *et al.* Pharmacokinetics and safety of propiverine in patients with fatty liver disease. *Eur J Clin Pharmacol* 1998; **54:** 767–71.

Urinary incontinence. Although propiverine is licensed in the UK for use in urinary frequency, urgency, and incontinence (see above), guidelines subsequently issued by NICE consider that although it should be an option for urinary frequency in women with overactive bladder syndrome, use in women with overt incontinence is not recommended.[1]

1. NICE. Urinary incontinence: the management of urinary incontinence in women (issued October 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/CG40NICEguideline.pdf (accessed 02/09/08)

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mictonetten; Mictonorm; ***Ger.:*** Mictonetten; Mictonorm; ***Jpn:*** BUP-4; ***Port.:*** Detrunorm†; Mictonorm; ***S.Afr.:*** Detrunorm; ***Thai.:*** Mictonorm; ***UK:*** Detrunorm.

Pygeum Africanum

African Prune; Afrikankirsikkapuunkuori (pygeum africanum bark); Afrikinių slyvų žievė (pygeum africanum bark); Kůra slivoně africké (pygeum africanum bark); Pruni Africanae; Pruni africanae cortex (pygeum africanum bark); Prunier d'Afrique; Prunier d'Afrique, écorce de (pygeum africanum bark).
ATC — G04CX01.
ATC Vet — QG04CX01.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*
Ph. Eur. 6.2 (Pygeum Africanum Bark; Pygeum Bark BP 2008). The whole or cut, dried bark of the stems and branches of *Prunus africana* (*Pygeum africanum*).
USP 31 (Pygeum). The bark of *Prunus africana* (*Pygeum africanum*) (Rosaceae). It contains not less than 9.0% of extractable matter.

Profile

An extract from the bark of the tree *Prunus africana* (*Pygeum africanum*) is used in the treatment of benign prostatic hyperplasia (p.2178). Like some other phytotherapies for this disorder, it appears to contain various sitosterols. A usual oral dosage is 100 mg daily.

Benign prostatic hyperplasia. Pygeum africanum appears to produce a modest benefit on urological symptoms and measures of urinary flow.

References.

1. Andro M-C, Riffaud J-P. Pygeum africanum extract for the treatment of patients with benign prostatic hyperplasia: a review of 25 years of published experience. *Curr Ther Res* 1995; **56:** 796–817.
2. Buck AC. Phytotherapy for the prostate. *Br J Urol* 1996; **78:** 325–36.
3. Ishani A, *et al.* Pygeum africanum for the treatment of patients with benign prostatic hyperplasia: a systematic review and quantitative meta-analysis. *Am J Med* 2000; **109:** 654–64.

Preparations

USP 31: Pygeum Capsules.

Proprietary Preparations (details are given in Part 3)
Austria: Tadenan; ***Braz.:*** Prostem; ***Cz.:*** Tadenan; ***Fr.:*** Tadenan; ***Gr.:*** Foudanil; Rotamat; Tadenan; ***Hung.:*** Tadenan†; ***Ital.:*** Pigenil; Tadenan; ***Mex.:*** Tadenom; ***Philipp.:*** Tadenan; ***Pol.:*** Poldanen; Tadenan; ***Port.:*** Tadenan†; ***Rus.:*** Tadenan (Таденан); Trianol (Трианол); ***Spain:*** Acubiron; Bidrolar; Pronitol; Tuzanil; ***Switz.:*** Tadenan; ***Thai.:*** Tadenan.

Multi-ingredient: ***Arg.:*** Catiz Plus; Normoprost Compuesto; Normoprost Plus; Ultracal; ***Austria:*** Prostatonin; ***Braz.:*** Prostem Plus; ***Canad.:*** Prostate Ease; Prostease; ***Cz.:*** Prostatonin†; ***Hong Kong:*** Prostease; ***Pol.:*** Neopoldanen; ***Port.:*** Neo Urgenin; ***Spain:*** Neo Urgenin; Prosturol; Tebetane Compuesto; ***Switz.:*** Prostatonin.

Saw Palmetto

American Dwarf Palm; *Brahea serrulata*; PA-109; Palmera de Florida; Sabal; Sabal, fruit de (saw palmetto fruit); *Sabal serrulata*; Sabalis Serrulatae; Sabalis serrulatae fructus (saw palmetto fruit); Sågpalmettofrukt (saw palmetto fruit); Sahapalmunhedelmä (saw palmetto fruit); *Serenoa repens*; *Serenoa serrulatum*; Serenový plod (saw palmetto fruit); Šliaužiančiųjų serenojų vaisiai (saw palmetto fruit).
ATC — G04CX02.
ATC Vet — QG04CX02.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*. *US* also includes the extract and the powdered form.
Ph. Eur. 6.2 (Saw Palmetto Fruit). The dried, ripe fruit of *Ser-*

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.

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.

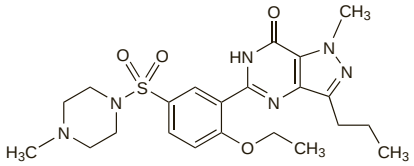
Сильденафила Цитрат

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