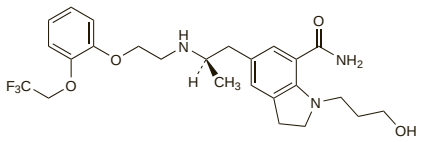
Silodosin *(rINN)*

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).

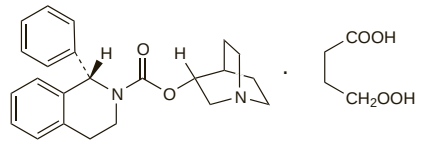
Солифенацина Суксинат

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

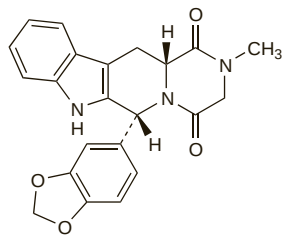
Тадалафил

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

◊ References.

1. Brock GB, *et al.* Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol (Baltimore)* 2002; **168:** 1332–6. Correction. *ibid.* 2005; **173:** 664. [dosage error in abstract]
2. Brock GB. Tadalafil: a new agent for erectile dysfunction. *Can J Urol* 2003; **10** (suppl 1): 17–22.
3. Bella AJ, Brock GB. Tadalafil in the treatment of erectile dysfunction. *Curr Urol Rep* 2003; **4:** 472–8.
4. Curran MP, Keating GM. Tadalafil. *Drugs* 2003; **63:** 2203–12. Correction. *ibid.*; 2703.
5. Meuleman EJ. Review of tadalafil in the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2003; **4:** 2049–56.
6. Padma-Nathan H. Efficacy and tolerability of tadalafil, a novel phosphodiesterase 5 inhibitor, in treatment of erectile dysfunction. *Am J Cardiol* 2003; **92** (suppl 1): 19M–25M.
7. Carson CC, *et al.* The efficacy and safety of tadalafil: an update. *BJU Int* 2004; **93:** 1276–81.
8. Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. *Expert Opin Pharmacother* 2005; **6:** 75–84.