Drugs 2003; 63 (20): 2203-2212
0012-6667/03/0020-2203/$33.00/0

Tadalafil

Monique P. Curran and *Gillian M. Keating*

Adis International Limited, Auckland, New Zealand

Contents

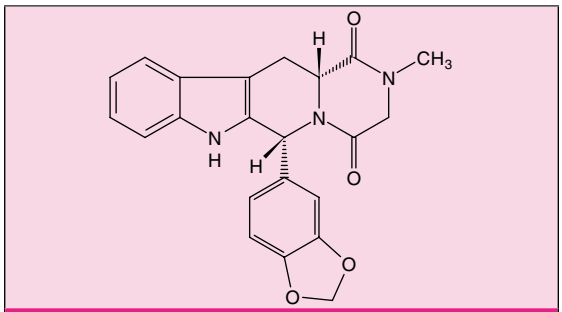
Abstract

▲ Tadalafil is a selective phosphodiesterase type 5 inhibitor that is effective in men with mild-to-severe erectile dysfunction (ED), including those with diabetes mellitus.

▲ The improvement in the erectile function domain score on the International Index of Erectile Function (IIEF) and the percentage of sexual intercourse attempts marked by successful vaginal penetration and completion was significantly greater with on-demand (not more than once daily) tadalafil 10 or 20mg than placebo in trials of 12 weeks' duration. Improvement in scores on other domains of the IIEF and the percentage of positive responses to a Global Assessment Question measuring erection improvement were also significantly greater with on-demand tadalafil than placebo.

▲ The adverse events associated with tadalafil were generally mild to moderate and decreased in frequency with continued administration. The most commonly reported adverse events were headache and dyspepsia. The incidence of cardiovascular adverse events was not significantly different in tadalafil or placebo recipients.

Features and properties of tadalafil (Cialis™)	
Indication	
Treatment of men with erectile dysfunction	
Mechanism of action	
Inhibits phosphodiesterase type 5 – an enzyme which hydrolyses cyclic guanosine monophosphate in the corpus cavernosum tissue of the penis	
Dosage and administration	
Recommended dose	10 or 20mg taken prior to anticipated sexual activity and without regard to food
Route of administration	Oral
Frequency of administration	Once daily (maximum)
Pharmacokinetics (oral administration of a single dose of 20mg)	
Mean peak plasma concentration	378 μg/L
Median time to peak plasma concentration	2h
Mean area under the plasma concentration-time curve	8066 μg • h/L
Mean elimination half-life	17.5h
Adverse events	
Most frequent	Headache and dyspepsia
Severity	Generally mild to moderate



Erectile dysfunction (ED), defined as the consistent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance, is estimated to affect up to 30 million men in the US.[1] ED is more common with advancing age[2-4] and may result from a number of age-related medical conditions (e.g. hypertension or diabetes mellitus) or use of certain pharmacological agents (e.g. antiarrhythmics and antihypertensives).[1] ED is distressing to patients and their partners and has an adverse effect on quality of life and social relationships.

An important development in the treatment of ED has been the discovery of drugs that inhibit the enzyme phosphodiesterase type 5 (PDE5), the first of which was sildenafil.[5] PDE5 is the predominant cyclic guanosine monophosphate (cGMP) hydrolysing enzyme in the penile corpus cavernosum.[6,7] When sexual stimulation causes the local release of nitric oxide, inhibition of PDE5 enhances the concentration of penile cGMP and potentiates smooth muscle relaxation in the corpus cavernosum. The resultant increased arterial blood flow leads to enlargement of the corpus cavernosum tissue. Veins are compressed between the corpus cavernosum and the tunica albuginea as a result of the increased tumescence, and the outflow of blood is reduced. Consequently, intracavernosal pressure increases and an erection occurs.[8]

This article reviews data on the use of tadalafil (Cialis™[1]), a new PDE5 inhibitor, in men with ED.

1. Pharmacodynamic Profile

Mechanism of Action

- Tadalafil is a selective inhibitor of PDE5. The concentration of tadalafil that inhibited 50% of the activity (IC_{50}) of isolated PDE5 was 0.9 nmol/L in an *in vitro* study (presented as an abstract).[9] The inhibition of PDE5 by tadalafil was 780-fold greater than that of the retinal enzyme PDE6 (IC_{50} 730 nmol/L)[9] and at least 9000-fold greater than that of other isoforms of human PDE (1–4 and 7–10),[9] but only 5-fold greater than that of PDE11.[10] The selectivity of tadalafil for PDE5 over PDE3 is important because PDE3 is an enzyme involved in cardiac contractility (see section 4).
- Tadalafil 30 nmol/L significantly potentiated the maximum relaxation of human trabecular smooth muscle induced by transmural electrical stimulation (67.4% vs 42.4% without tadalafil at 6Hz; $p < 0.005$).[9] In addition, tadalafil 30 nmol/L significantly potentiated sodium nitroprusside-induced accumulation of cGMP in human cavernosal tissue (0.99 vs 0.47 pmol/mg protein; $p < 0.05$) and significantly potentiated the relaxation of penile smooth muscle induced by acetylcholine ($p < 0.004$).[9]

Effects on Penile Erection

- In a proof-of-concept study, the mean increase in maximum rigidity of the base of the penis was greater with tadalafil 100mg (15.2%) than placebo (2.6%; $p \leq 0.008$) administration in 44 men with mild-to-moderate ED.[11] In this double-blind, crossover study (presented as an abstract), the men under-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

went RigiScan™ penile plethysmography during visual sexual stimulation. The increase in rigidity of the penis at the tip was also greater with tadalafil 100mg than placebo ($p \leq 0.001$) administration. The mean increase in duration of erection (≥55% rigidity at the base of the penis) was 1.4 minutes in placebo recipients and 9.3 minutes in recipients of tadalafil 100mg ($p \leq 0.001$).[11]

Period of Responsiveness

European labelling for tadalafil indicates that the drug may be effective for up to 24 hours.[12] Although data on responsiveness beyond 24 hours are available,[13,14] this section reviews only data up to this timepoint (i.e. in line with European labelling). It should be noted that some regional labelling may differ from Europe in this respect.

- The erectile response (≥55% rigidity at the base of the penis for ≥3 consecutive minutes) was significantly greater with tadalafil 10mg than placebo at 45 minutes ($p = 0.034$) and at 24 hours ($p = 0.001$) after single-dose administration.[15] This multicentre, randomised, double-blind, crossover study (presented as an abstract and poster) involved 61 men with ED of ≥3 months' duration. Erectile response was assessed by RigiScan™ penile plethysmography during visual sexual stimulation. At 24 hours after dose administration, 59% of tadalafil recipients compared with 7% of placebo recipients were able to achieve an erectile response ($p = 0.001$). At 24 hours after dose administration, the mean cumulative time with an erectile response was 11 minutes with tadalafil compared with 1 minute with placebo ($p = 0.001$).[15]
- At 16 minutes after dosing, the percentage of intercourse attempts that were successful (assessed according to Sexual Encounter Profile question 3 [SEP-Q3]) was significantly greater in recipients of a single dose of tadalafil 20mg (32%) than in placebo recipients (15%; $p = 0.012$) in a randomised, double-blind study involving 223 men with mild-to-severe ED of ≥3 months' duration conducted in the home setting (data presented in an abstract).[15] The men received a single dose of tadalafil or placebo every 8 to 10 days (total of 4 doses) when ready to engage in sexual activity. With tadalafil 20mg, the mean time for achievement of an erection was 17 minutes in responders (patients able to have at least one erection sufficient for successful sexual intercourse within 30 minutes of receiving the study drug).
- Similarly, the percentage of the 227 intercourse attempts that were successful (assessed according to SEP-Q3) at 24 hours after administration was greater with a single dose of tadalafil 20mg than with placebo (53% vs 29%; both $p < 0.001$) in a randomised, double-blind study in 348 men with mild-to-severe ED.[13]
- In an integrated analysis of five randomised, double-blind trials in men with ED ($n = 1112$) of 12 weeks' duration, the percentage of successful intercourse attempts after a single dose of tadalafil 20mg (measured by SEP-Q3) was 39% in the first 30 minutes, 73% for 30 minutes to 4 hours and 80% from 4 hours to 24 hours.[14]

Effects on Cardiovascular Parameters

- There were no significant between-group differences in the mean maximal changes from baseline in standing systolic and diastolic blood pressure (BP) in 33 recipients of a single oral dose of tadalafil 20mg and 15 recipients of placebo (mean difference −0.2/−4.6mm Hg) in a randomised, double-blind study in men with ED (data reported in an abstract and poster).[16] Although, the between-group difference in the mean maximal changes from baseline in standing systolic BP in 32 recipients of a tadalafil 10mg and placebo was statistically significantly different (+1.3mm Hg), the difference was not considered to be clinically relevant by the researchers. There was no between-group difference in diastolic BP (−2.6mm Hg). There was no statistically signif-

icant difference in heart rate after treatment with tadalafil (10 or 20mg) or placebo. See section 4 for details of the cardiovascular adverse event profile in tadalafil recipients.

- In a pooled analysis of data from 1328 men with mild to severe ED treated with tadalafil 2.5–20mg or placebo in six phase III trials,[16] there were no statistically or clinically significant between-group differences in the mean changes from baseline to endpoint in systolic and diastolic BP and heart rate.

- There was no significant-between group difference in the time to ischaemia during exercise stress testing in men with stable coronary artery disease treated with tadalafil 10mg or placebo approximately 2–2.5 hours previously (data reported in an abstract).[17] The randomised, double-blind, crossover trial involved 23 men (aged 53–75 years) who demonstrated ischaemia during a screening exercise stress test (≥5 metabolic equivalents). The time to limiting ischaemia (≥1.5mm ST depression in ≥2 contiguous leads, and/or until limited by symptoms of cardiac ischaemia with ≥1.5mm ST depression on continuous ECG recording) after 13 minutes of exercise was 31 and 36 seconds in recipients of tadalafil 10mg and placebo, respectively. Changes in BP and heart rate were similar in tadalafil and placebo recipients.

- Co-administration of tadalafil 20mg and alcohol (0.6 g/kg taken 2 hours after the tadalafil dose) had no clinically significant effect on maximum standing or supine systolic/diastolic BP or heart rate in a placebo-controlled crossover study in 48 healthy male volunteers (aged 18–60 years).[18] The between-group difference in the least-squares mean maximum decrease in standing systolic/diastolic BP in tadalafil/alcohol and placebo/alcohol recipients was 3.2/0.3mm Hg. The between-group difference in the least-squares mean maximum increase in standing heart rate was 4.1 beats per minute.

Interactions with Nitrates

- Tadalafil had a minimal effect, relative to placebo, on the mean maximal change in standing systolic BP (MMCSBP) induced by sublingual or long-acting nitroglycerin (the primary endpoint) in randomised, double-blind, crossover trials (data presented in abstracts) in healthy volunteers[19] or in patients with stable angina pectoris.[20] In a study in 49 healthy volunteers aged >55 years, there was no significant difference in the MMCSBP induced by sublingual nitroglycerin with tadalafil 10mg or placebo administration.[19] In patients with stable angina, the MMCSBP versus placebo after administration of sublingual nitroglycerin (n = 51) or daily long-acting nitroglycerin (n = 45) was −3 and −2mm Hg with tadalafil 10mg and −8 ($p < 0.05$) and 0mm Hg with tadalafil 5mg.[20]

- However, tadalafil augmented the decrease in BP induced by nitrates in a subset of patients with angina[20] and healthy volunteers[19] (see figure 1 for the number of men with standing systolic BP <85mm Hg [outliers] after administration of sublingual[19,20] or long-acting nitroglycerin[20]). There was no significant between-group difference in the number of outliers following tadalafil 10mg or sildenafil administration in the study in healthy volunteers.[19]

2. Pharmacokinetic Profile

- Noncompartmental pharmacokinetic parameters of a single dose of oral tadalafil 10 or 20mg were determined in an integrated analysis (presented as an abstract) of 13 studies involving a total of 237 healthy volunteers.[21] The dose-dependent parameters for the 10mg dose were normalised to 20mg. Tadalafil 20mg was rapidly absorbed following oral administration with a mean maximum plasma concentration of 378 μg/L occurring at a median of 2 hours; the mean area under the plasma concentration-time curve (AUC) was 8066 μg • h/L.[22] The mean apparent volume of distribution was 62.6L.

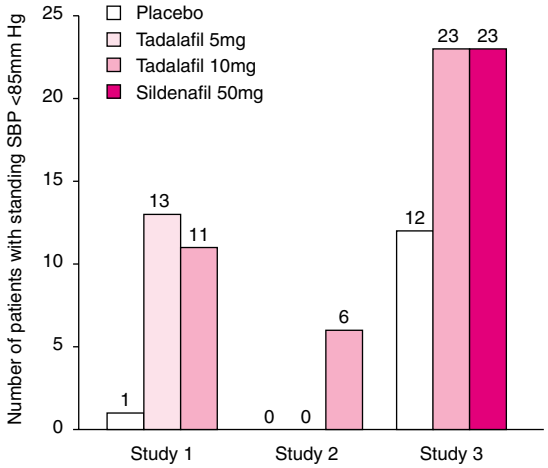


Fig. 1. The number of recipients of tadalafil, sildenafil or placebo with standing systolic BP (SBP) <85mm Hg after administration of sublingual nitroglycerin or long-acting nitroglycerin in randomised, double-blind, crossover studies.[19,20] Tadalafil 5 or 10mg or placebo was administered to 51 patients with stable angina 2 hours before administration of sublingual nitroglycerin (study 1) or to 45 patients with stable angina during daily long-acting nitroglycerin therapy (study 2).[20] In study 3,[19] 49 healthy volunteers (aged >55 years) were administered sublingual nitroglycerin following tadalafil 10mg, sildenafil 50mg or placebo treatment.

The mean elimination half-life ($t_{1/2}$) for tadalafil was 17.5 hours and the mean apparent oral clearance was 2.48 L/h.

- Tadalafil is primarily metabolised by the cytochrome P450 3A4. The primary metabolite is methylcatechol glucuronide, which has ≥13 000-fold less affinity for PDE5 than tadalafil, and is consequently not clinically active.[23]
- Neither age nor gender had a statistically significant effect on the pharmacokinetics of tadalafil (dosage not clearly stated), according to data presented in a poster.[23] The tadalafil AUC in healthy volunteers aged >65 years (n = 12) was 25% greater than that for volunteers aged 18–65 years (n = 12). This was associated with a longer $t_{1/2}$ in elderly than young volunteers (21.6 vs 16.9 hours). However, these differences were not statistically significant and were not considered to be clinically significant by the researchers.[23]
- The tadalafil AUC was reduced (19%) and the $t_{1/2}$ was shorter in patients with diabetes mellitus (n = 13) than in those without diabetes mellitus (n = not stated).[23] However, these differences were not statistically significant and were not considered to be clinically significant.[23]
- Mild (creatinine clearance 51–80 mL/min) or moderate (creatinine clearance 31–50 mL/min) renal impairment or hepatic impairment (Child-Pugh Class A and B) did not alter the pharmacokinetic parameters of tadalafil (statistical significance not determined).[23]
- Food did not alter the rate and extent of absorption of a single dose of tadalafil 20mg in healthy volunteers (n = 18).[23]

3. Therapeutic Efficacy

The therapeutic efficacy of on-demand tadalafil (taken as required, but no more than once daily) has been investigated in randomised, double-blind, placebo-controlled trials in patients with mild-to-severe ED.[14,24-26] Although two early 3- (n = 179)[25] and 8-week (n = 212)[26] phase II studies investigated the efficacy of on-demand tadalafil 2–25mg in patients with mild-to-severe ED, this section focuses on the efficacy of tadalafil 10 and 20mg, as reported in the phase III trials.[14,24]

Phase III studies of 12 weeks' duration have investigated the efficacy of on-demand tadalafil in men with a minimum 3-month history of ED associated with diabetes mellitus[24] or various etiologies.[14] One study investigated the effects of on-demand tadalafil 10 or 20mg in 216 men (mean age 56 years) with type 1 or type 2 diabetes mellitus.[24] In addition, a pooled analysis of five studies reported the effects of on-demand tadalafil 2.5–20mg in 1112 men with ED (mean age 59 years) of various etiologies (organic [61%], psychogenic [9%] or mixed [31%]).[14] The men were free to choose the time of sexual activity attempts, and were able to

take tadalafil without restrictions on food and alcohol intake.[14,24]

The efficacy of tadalafil was evaluated using the International Index of Erectile Function (IIEF) questionnaire, SEP diary data and a Global Assessment Question (GAQ; "Has the treatment you have been taking improved your erections?").[14,24]

The IIEF is a self-measured 15-item questionnaire[27] that assessed five domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction).[27] Responses to the questions were scored on a categoric scale (response options of 0 [did not attempt intercourse] and 1 [almost never/never] to 5 [almost always/always]).[27]

Primary efficacy was measured by the changes from baseline in the erectile function domain of the IIEF and changes from baseline in the proportion of 'yes' responses to question 2 (Q2: "Were you able to insert your penis into your partner's vagina?") and question 3 (Q3: "Did your erection last long enough for you to have successful intercourse") of the SEP.[14,24]

Baseline values of the above efficacy assessments were collected during a 4-week treatment-free run-in period.[14,24]

International Index of Erectile Function

- Erectile function (assessed by the IIEF erectile function domain score) was improved from baseline to a significantly greater extent with tadalafil 10 or 20mg than placebo ($p < 0.001$; see figure 2) in men with ED of various etiologies[14] and in men with ED associated with diabetes mellitus.[24] Lower doses of tadalafil (2.5 and 5mg) were also significantly more effective than placebo ($p < 0.05$; see figure 2) in men with ED of various etiologies.[14] In patients with diabetes mellitus,[24] this improvement was independent of baseline glycosylated haemoglobin (HbA_{1c}) level.

- The mean improvements in IIEF scores on a question relating to penetration ability (Q3) and a question relating to maintenance ability (Q4) were significantly greater versus placebo in a 12-week trial in men with ED and diabetes mellitus who received on-demand tadalafil 10 and 20mg ($p < 0.001$).[24]

- The number of patients who achieved normal erectile function (IIEF erectile function domain score ≥26) at endpoint was significantly greater with tadalafil 10 or 20mg (40% and 59%) than with placebo (11%; $p < 0.001$) in men with mild to severe erectile dysfunction of various etiologies.[14]

- Mean IIEF intercourse satisfaction domain scores and overall satisfaction domain scores were improved to a greater extent with on-demand tadalafil 10 and 20mg, compared with placebo, in men with ED of various etiologies ($p < 0.001$)[14] and in men with ED associated with diabetes mellitus ($p < 0.05$).[24]

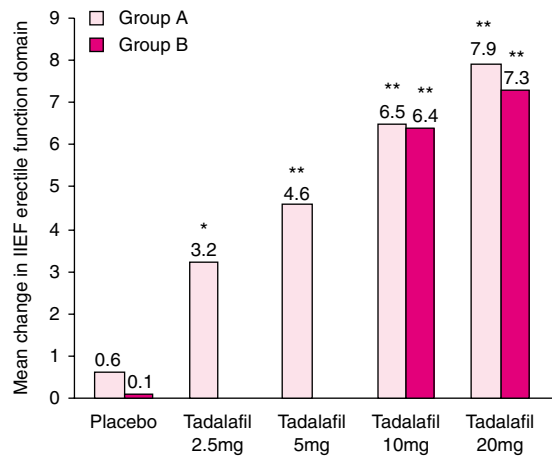


Fig. 2. Mean change in International Index of Erectile Function (IIEF) erectile function domain in men with a minimum 3-month history of erectile dysfunction (ED) in 12-week multicentre, randomised, double-blind studies. Group A included 1112 men with mild-to-severe ED of various etiologies randomised to placebo or on-demand (taken as needed, but no more than once daily) tadalafil at doses of 2.5, 5, 10 or 20mg in an integrated analysis of five studies.[14] Group B included 216 men with ED and type 1 or 2 diabetes mellitus randomised to placebo or on-demand tadalafil 10 or 20mg.[24] * $p < 0.05$, ** $p < 0.001$ vs placebo.

Sexual Encounter Profile

● The proportion of sexual attempts marked by successful vaginal penetration (SEP-Q2) and intercourse completion (SEP-Q3) was significantly greater with on-demand tadalafil 10 and 20mg than placebo treatment in men with ED of various etiologies[14] ($p < 0.001$; see figure 3) and in men with ED associated with diabetes mellitus.[24] In men with ED associated with diabetes mellitus,[24] the mean change in SEP-Q2 was −4.1%, +22.2% and +22.6% with placebo or tadalafil 10 or 20mg, respectively; the mean change in SEP-Q3 was +1.9%, +28.4% and +29.1%, respectively. Baseline HbA_{1c} did not influence response to tadalafil treatment.[24]

Global Assessment Questions

● Tadalafil significantly enhanced patients' erections according to the GAQ.[14,24] In a study involving men with ED of various etiologies,[14] the proportion of positive responses to the GAQ was 67% and 81% in recipients of on-demand tadalafil 10 and 20mg administration versus 35% in placebo recipients ($p < 0.001$). Lower doses of tadalafil (2.5 and 5mg) were also more effective than placebo ($p < 0.05$).[14] In 216 men with ED associated with diabetes mellitus, the proportion of positive responses to the GAQ was 56% and 64% in recipients of on-demand tadalafil 10 and 20mg versus 25% in placebo recipients (both $p < 0.001$).[24]

Effect of Age and of Erectile Dysfunction Etiology or Severity

● The efficacy of on-demand tadalafil 10 and 20mg was similar in men aged >65 years to that in men aged ≤65 years.[14,28]

● On-demand tadalafil 10 and 20mg improved erectile function to a greater extent in patients with severe ED than in those with mild ED, although the between-group statistical significance was not stated.[14] The mean change from baseline in IIEF erectile function domain scores was 8.7 and 12.2 in patients with severe ED (baseline IIEF erectile function domain score of 1–10), 8.9 and 10.4 in patients with moderate ED (baseline IIEF erectile function domain score of 11–16) and 3.3 and 4.7 in patients with mild ED (baseline IIEF erectile function domain score of 17–30) [$p < 0.001$ vs baseline for all tadalafil groups].[14]

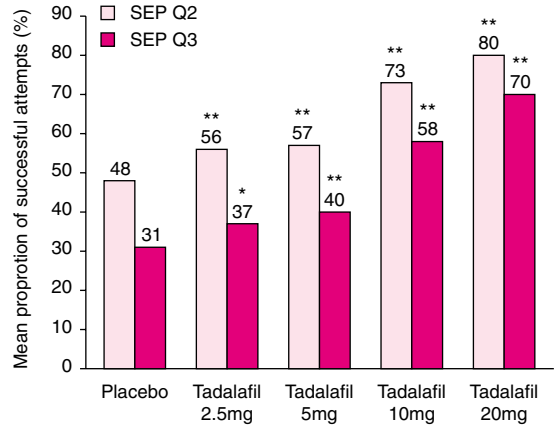


Fig. 3. Proportion of sexual intercourse attempts marked by successful penetration (Sexual Encounter Profile question 2 [SEP-Q2]) and intercourse completion (Sexual Encounter Profile question 3 [SEP-Q3]). The study involved 1112 men with mild-to-severe erectile dysfunction of various etiologies randomised to placebo or on-demand (taken as needed, but no more than once daily) tadalafil at doses of 2.5, 5, 10 or 20mg in an integrated analysis of five studies.[14] * $p < 0.05$, ** $p < 0.001$ vs placebo.

● On-demand tadalafil 10 and 20mg improved erectile function to a similar extent irrespective of the type of diabetes, the presence of microvascular complications or type of antihyperglycaemic treatment.[24]

4. Tolerability

● Adverse events associated with tadalafil in men with ED with or without diabetes mellitus were those commonly associated with PDE5 inhibitors, according to data from an integrated analysis of five 12-week, randomised, double-blind, multicentre trials (n = 1112; see figure 4).[14] Headache and dyspepsia were the most commonly reported treat-

ment-emergent adverse events (see figure 4). Adverse events were generally mild to moderate in intensity, transient and decreased in frequency with continued dosing. Discontinuation rates in recipients of tadalafil and placebo were low (2 and 1%, respectively). No clinically significant laboratory abnormalities or ECG changes were reported in tadalafil recipients. One tadalafil recipient (0.1%) reported an episode of abnormal colour vision.[14]

- Tadalafil was associated with good long-term tolerability, according to preliminary data (presented in an abstract) from an open-label, randomised extension of five 12-week, double-blind, multicentre trials (n = 1173).[29] Patients were initiated on tadalafil 10mg once daily, but titration to 20mg once daily was permissible. During the study, 870 patients received tadalafil ≥10mg once daily and 574 patients received tadalafil 20mg once daily for at least one year. Headache (15%) and dyspepsia (11%) were the most commonly reported adverse events. Overall 5% of tadalafil recipients discontinued because of adverse events.

- In a pooled analysis of phase III trials (presented in an abstract) in men with ED, including those with a variety of stable cardiovascular conditions and those on multiple antihypertensives,[30] the incidence of cardiovascular adverse events in recipients of tadalafil (n = 949) and placebo (n = 379) was low, with no significant between-group differences (e.g. flushing [4% and 2%], dizziness [both 2%], hypertension [1% and 2%] and syncope [0.1% and 0.5%]). Across all clinical trials, the incidence of myocardial infarction was 0.39 and 1.1 per 100 patient-years in tadalafil recipients (n >4000) and placebo recipients (n >1200), respectively.[30]

- The proportion of men showing a ≥50% decrease in sperm concentration was similar in healthy men with ED (n = 421) treated with once-daily tadalafil 10 or 20mg or placebo, according to data from two separate 6-month randomised, studies (presented in one abstract).[31] Tadalafil 10 or 20mg once daily had no adverse effects on sperm count per ejaculate, percentage normal sperm motility or morphology or serum levels of reproductive hormones. The men were aged ≥45 years and met WHO reference values for semen characteristics (sperm concentration ≥20 × 10^6/mL, >50% motility, >50% normal morphology).

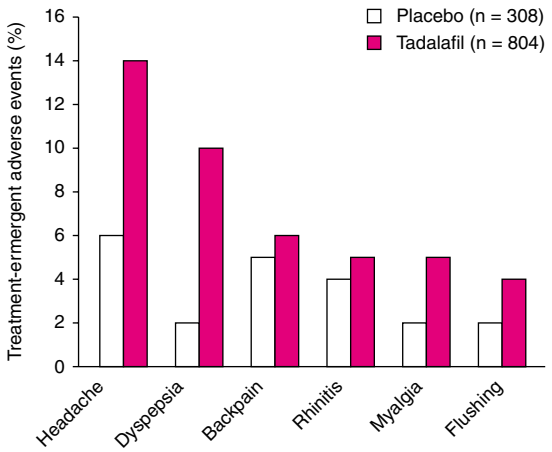


Fig. 4. Treatment-related adverse events reported in patients with erectile dysfunction of various etiologies. Patients (n = 1112) were randomised to tadalafil 2.5–20mg (taken as needed, but not more than once daily) or placebo in five 12-week double-blind, multicentre studies (data from a pooled analysis).[14]

5. Dosage and Administration

The recommended dose for tadalafil is 10mg prior to sexual activity and without regard to food. In men for whom the 10mg dose does not produce an adequate effect, a 20mg dose may be taken.[12] Tadalafil can be taken from 30 minutes to 12 hours prior to sexual activity, but sexual activity is required for the drug to take effect. The recommended dose of tadalafil in men with impaired renal or hepatic function is 10mg once daily. The efficacy of tadalafil may persist for up to 24 hours post dose (European labelling information).[12]

Tadalafil should not be taken in combination with any form of organic nitrate. Tadalafil should not be administered to patients with serious heart disease, myocardial infarction within the last 90

days, unstable angina or angina occurring during sexual intercourse, New York Heart Association Class 2 or greater heart failure in the last 6 months, uncontrolled hypertension or hypotension (<90/50mm Hg), uncontrolled arrhythmias or a stroke within the last 6 months.[12]

6. Tadalafil: Current Status

Tadalafil has been approved for marketing in Europe and in Australasia, and has received an approvable letter from the US FDA. It has shown clinical efficacy in patients with mild-to-severe ED,[14,24-26] including those with diabetes mellitus,[24] enabling men to have successful sexual intercourse. Tadalafil was well tolerated and adverse events were generally of mild-to-moderate intensity.

References

1. NIH Consensus Development Panel on Impotence. Impotence. JAMA 1993 Jul 7; 270: 83-90
2. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994 Jan; 151 (1): 54-61
3. Marumo K, Nakashima J, Murai M. Age-related prevalence of erectile dysfunction in Japan: assessment by the International Index of Erectile Function. Int J Urol 2001 Feb; 8 (2): 53-9
4. Blanker MH, Bosch JL, Groeneveld FP, et al. Erectile and ejaculatory dysfunction in a community-based sample of men 50 to 78 years old: prevalence, concern, and relation to sexual activity. Urology 2001 Apr; 57 (4): 763-8
5. Langtry HD, Markham A. Sildenafil; a review of its use in erectile dysfunction. Drugs 1999; 57: 967-87
6. Eardley I. New oral therapies for the treatment of erectile dysfunction. Br J Urol 1998 Jan; 81: 122-7
7. Truss MC, Stief CG. Phosphodiesterase inhibitors in the treatment of erectile dysfunction. Drugs Today 1998 Sep; 34: 805-12
8. Rotella DP. Phosphodiesterase type 5 inhibitors: discovery and therapeutic utility. Drugs Future 2001; 26 (2): 153-62
9. Angulo J, Gadau M, Fernandez A, et al. IC351 enhances nitric oxide-mediated relaxation of human arterial and trabecular penile smooth muscle [abstract no. 1133 plus poster]. Diabetologia 2001; 44 Suppl. 1: A295
10. Gbekor E, Bethell S, Fawcett L, et al. Phosphodiesterase 5 inhibitor profiles against all human phosphodiesterase families: implications for use as pharmacological tools [abstract no. 967]. J Urol 2002; 167 Suppl. 4: 246
11. Meuleman E, Lycklama NGL, Slob K, et al. Effects of IC351 on erectile response to visual sexual stimulation. J Urol 1999 Apr; 161 Suppl.: 212
12. Lilly ICOS Limited. Tadalafil (Cialis™): summary of product characteristics. London: Lilly ICOS Limited, 2003
13. Porst H, Padma-Natham H, Giuliano F, et al. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomised controlled study. Urology 2003; 62: 121-6
14. Brock GB, McMahon CG, Chen KK, et al. Efficacy and safety of tadalafil in men with erectile dysfunction: results of integrated analysis. J Urol 2002; 168: 1332-6
15. Padma-Nathan H, Rosen RC, Shabsigh R, et al. Cialis™ (IC351) provides prompt response and extended period of responsiveness for the treatment of men with erectile dysfunction. J Urol 2001 May; 165 Suppl.: 224
16. Hutter Jr AM, Kloner RA, Watkins VS, et al. Blood pressure and cardiovascular effects of tadalafil, a new PDE5 inhibitor [abstract no. P-302 plus poster]. Am J Hypertens 2002; 15 (Pt 2): 140
17. Patterson D, MacDonald TM, Effron MB, et al. Tadalafil does not affect time to ischemia during exercise stress testing in patients with coronary artery disease [abstract no. 1650]. Circulation 2002; 106 (19 Suppl. II): 330
18. Mitchell M, Sanderson B, Payne C, et al. Pharmacodynamic interaction between alcohol and tadalafil in healthy volunteers [abstract no. P-112]. Proceedings of the 5th Congress of the European Society for Sexual and Impotence Research; 2002 Dec 1-4; Hamburg
19. Kloner RA, Mitchell MI, Bedding A, et al. Pharmacodynamic interactions between tadalafil and nitrates compared with sildenafil [abstract no. 708]. J Urol 2002; 167 Suppl.: 176
20. Kloner R, Emmick J, Bedding A, et al. Pharmacodynamic interactions between tadalafil and nitrates [abstract no. 1051-30]. J Am Coll Cardiol 2002; 39 Suppl. A: 291A
21. Patterson B, Bedding A, Jewell H, et al. Dose-normalised pharmacokinetics of tadalafil administered as a single dose to healthy volunteers [abstract no. 600]. Eur Urol 2002; 41 Suppl. 1: 152
22. Porst H. IC351 (tadalafil, Cialis): update on clinical experience. Int J Impot Res 2002 Feb; 14 Suppl. 1: S57-64
23. Patterson B, Bedding A, Jewell H, et al. The effect of intrinsic and extrinsic factors on the pharmacokinetic properties of tadalafil (IC351) [abstract plus poster]. Proceedings of the 4th Congress of the European Society for Sexual and Impotence Research; 2001 Sep 30-Oct 3; Rome
24. Sáenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002; 25 (12): 2159-64
25. Padma-Nathan H, McMurray JG, Pullman WE, et al. On-demand IC351 (Cialis™) enhances erectile function in patients with erectile dysfunction. Int J Impot Res 2001 Feb; 13 (1): 2-9
26. Anglin G, Iglesias J, Toulouse K, et al. Efficacy and safety of IC351 treatment for erectile dysfunction [abstract no. B8]. Int J Impot Res 2000; 12 Suppl. 3: S75

27. Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49 (6): 822-30
28. Nash DT. The safety and efficacy of tadalafil in elderly men with ED [abstract no. 48]. Am J Geriatr Cardiol 2003; 12 (2): 138-9
29. Montorsi F, Verheyden B, Junemann K-P, et al. Long-term safety experience with tadalafil [abstract no. 947]. J Urol 2003; 169 Suppl. 4: 245
30. Kloner RA, Watkins VS, Costigan TM, et al. Cardiovascular profile of tadalafil, a new PDE5 inhibitor [abstract no. 707]. J Urol 2002; 167 Suppl.: 176
31. Hellstrom W, Overstreet JW, Yu A, et al. Tadalafil has no effect on spermatogenesis or reproductive hormones [abstract no. 948]. 2003; 169 (4 Suppl.): 245

Correspondence: *Monique P. Curran*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz