

*Be ready anytime
the moment is right.*



PROCIAL[®] 5 mg

Tadalafil

For the treatment of ED, BPH and BPH+ ED

Once Daily

Procial® 5 mg is an option for most men with ED:¹

Wants to remove time concern²

Wants to restore spontaneity³

Wants to go back to life like before ED²

Who may have a variety of comorbidities (diabetes, hypertension, hyperlipidemia etc..)^{2,4,5}



Any age*

All levels of severity of ED⁵

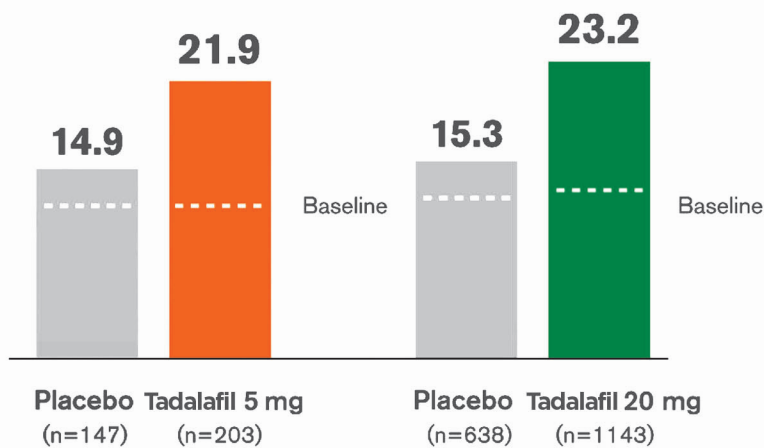
Has regular intimacy²

Wants to regain sexual confidence³

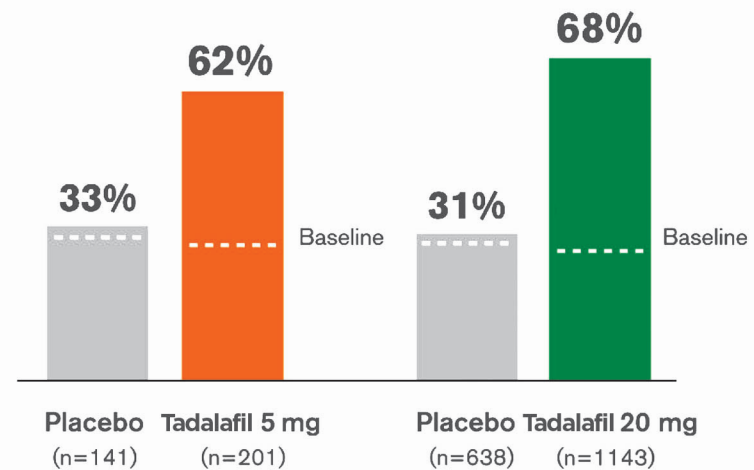
*(\geq 18 years of age)

Efficacy of Tadalafil 5 mg (once daily) VS. Tadalafil 20 mg (on demand) was shown to be consistent⁶

Mean IIEF[†]-EF domain scores^{6,7}



Mean percent positive responses^{6,7} Successful completion of intercourse (SEP3[‡])

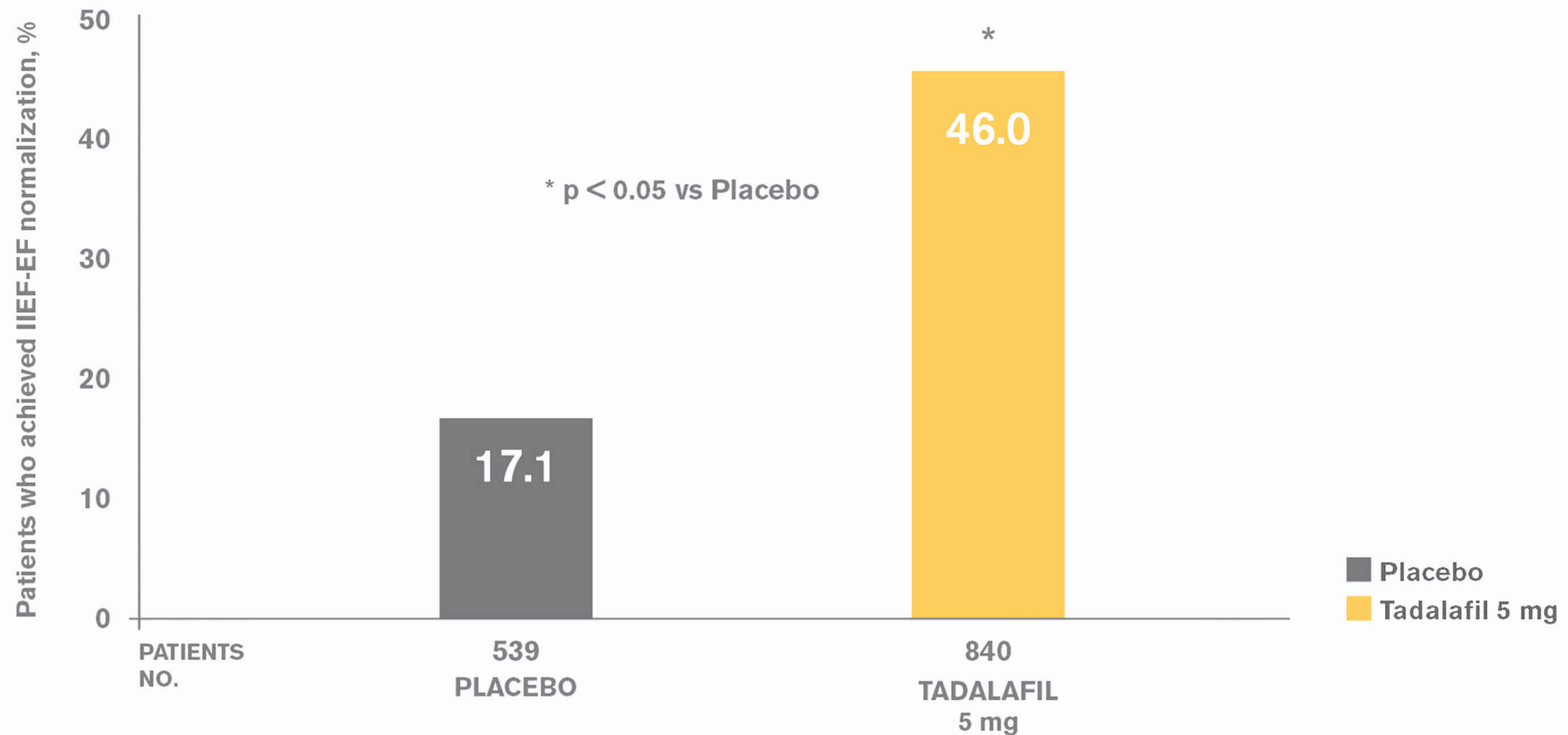


* p<0.01 mean change after treatment

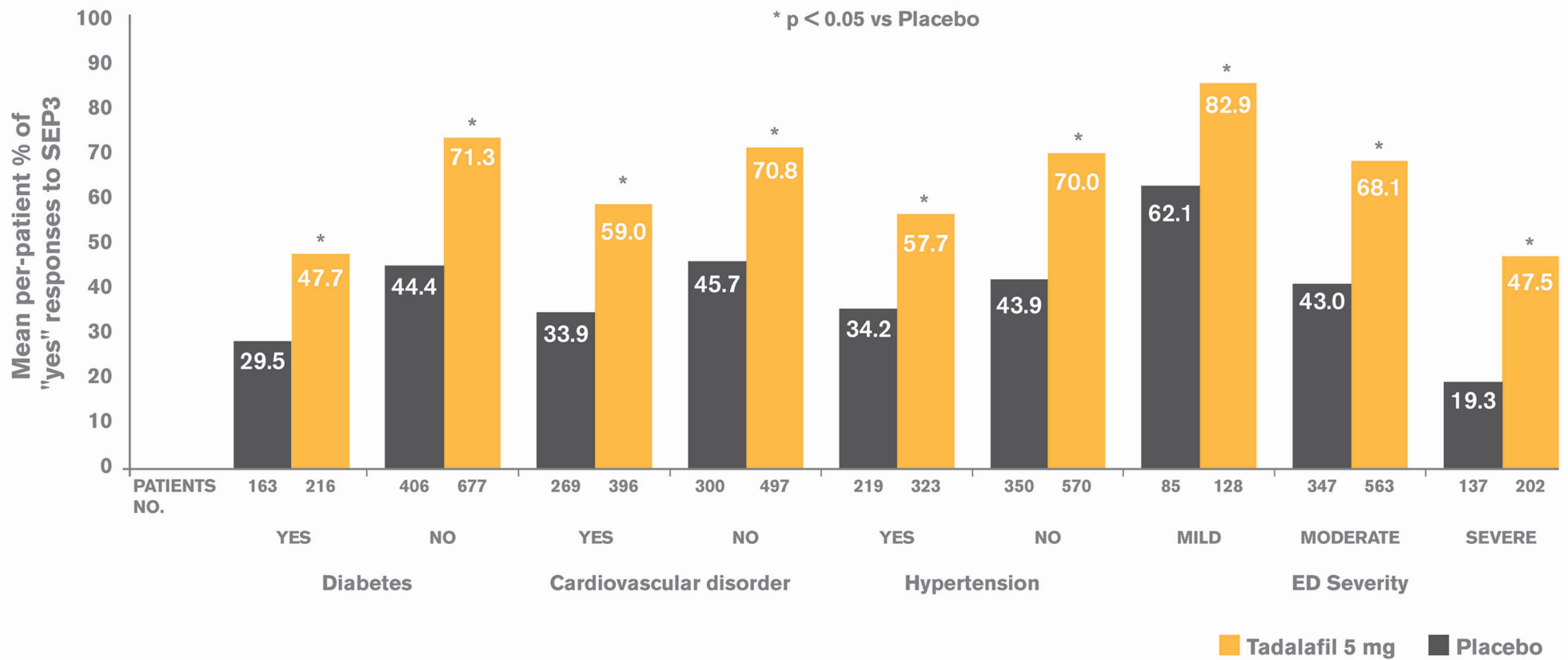
† International Index of Erectile Function

‡ SEP3: Did your erection last long enough for sexual intercourse?

Treatment with Tadalafil 5 mg once daily was important improvements across different



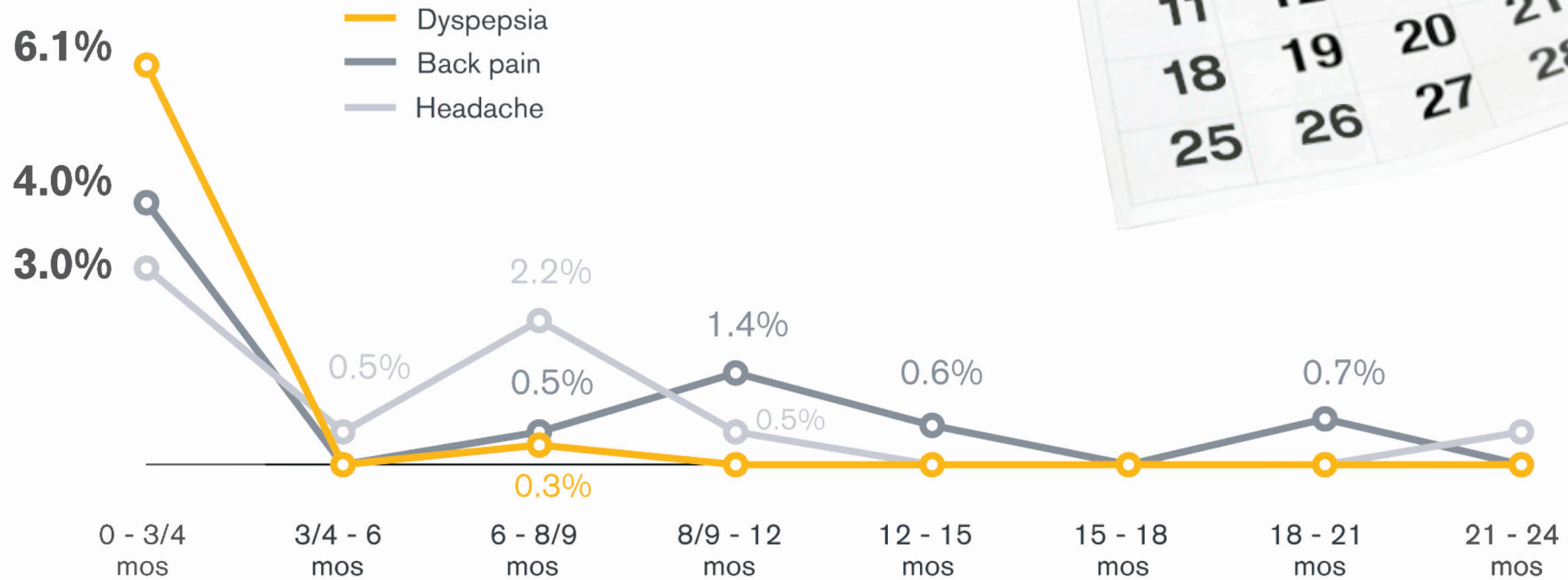
well tolerated and resulted in clinically subpopulations of patients⁸



Tadalafil 5 mg was well-tolerated in the long term⁹



Incidence of Side Effects



Tadalafil 5 mg was well tolerated and effective, making it a viable alternative to the current on-demand dosing of tadalafil for men with ED⁹.



Drug Description: Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). **Therapeutic indications:** Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), Treatment of ED and the signs and symptoms of BPH (ED/BPH) . **Posology and method of administration:** Tadalafil tablets should be swallowed whole. Tadalafil may be taken with or without meals. **Contraindications:** Administration of Tadalafil to patients using any form of organic nitrate is contraindicated. Tadalafil was shown to potentiate the hypotensive effect of nitrates. History of known serious hypersensitivity reaction to Tadalafil. Administration with guanylate cyclase (GC) stimulators, such as Riociguat. **Special warnings and precautions for use:** Patients should not use Tadalafil if sex is inadvisable due to cardiovascular status. Use of Tadalafil with alpha-blockers, antihypertensives or substantial amounts of alcohol (≥ 5 units) may lead to hypotension. Tadalafil is not recommended in combination with alpha-blockers for the treatment of BPH. Caution is advised when Tadalafil is used as a treatment for ED in men taking alpha-blockers. Patients should seek emergency treatment if an erection lasts >4 hours. Use Tadalafil with caution in patients predisposed to priapism. Patients should stop Tadalafil and seek medical care if a sudden loss of vision occurs in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). Tadalafil should be used with caution, and only when the anticipated benefits outweigh the risks, in patients with a history of NAION. Patients with a "crowded" optic disc may also be at an increased risk of NAION. Patients should stop Tadalafil and seek prompt medical attention in the event of sudden decrease or loss of hearing. Consideration should be given to other urological conditions that may cause similar symptoms. **Interaction with other medicinal products and other forms of interaction: Potential for Pharmacodynamic Interactions with Tadalafil: Nitrates** — Administration of Tadalafil to patients who are using any form of organic nitrate, is contraindicated. **Alpha-Blockers** — Caution is advised when PDE5 inhibitors are co administered with alpha-blockers. **Antihypertensives** — PDE5 inhibitors, including tadalafil, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendrofluazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo. **Alcohol** — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood-pressure-lowering effects of each individual compound may be increased. **Potential for Other Drugs to Affect Tadalafil: Antacids** — Simultaneous administration of an antacid (magnesium hydroxide/aluminum hydroxide) and tadalafil reduced the apparent rate of absorption of tadalafil without altering exposure (AUC) to tadalafil. **H2 Antagonists (e.g. Nizatidine)**. An increase in gastric pH resulting from administration of nizatidine had no significant effect on pharmacokinetics. **Cytochrome P450 Inhibitors** — Tadalafil is a substrate of and predominantly metabolized by CYP3A4. Studies have shown that drugs that inhibit CYP3A4 can increase tadalafil exposure. **CYP3A4 (e.g., Ketoconazole)** — Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4, increased tadalafil 20 mg single-dose exposure (AUC) by 312% and Cmax by 22%, relative to the values for tadalafil 20 mg alone. Ketoconazole (200 mg daily) increased tadalafil 10-mg single-dose exposure (AUC) by 107% and Cmax by 15%, relative to other CYP3A4 inhibitors, such as erythromycin, itraconazole, and grapefruit juice, would likely increase tadalafil exposure. **HIV Protease Inhibitor** — Ritonavir (500 mg or 600 mg twice daily at steady state), an inhibitor of CYP3A4, CYP2C9, CYP2C19, and CYP2D6, increased tadalafil 20-mg single-dose exposure (AUC) by 32% with a 30% reduction in Cmax, relative to the values for tadalafil 20 mg alone. Ritonavir (200 mg twice daily), increased tadalafil 20-mg single dose exposure (AUC) by 124% with no change in Cmax, relative to the values for tadalafil 20 mg alone. Although specific interactions have not been studied, other HIV protease inhibitors would likely increase tadalafil exposure. **Cytochrome P450 Inducers** — Studies have shown that drugs that induce CYP3A4 can decrease tadalafil exposure. **CYP3A4 (e.g., Rifampin)** — Rifampin (600 mg daily), a CYP3A4 inducer, reduced tadalafil 10-mg single-dose exposure (AUC) by 88% and Cmax by 46%, relative to the values for tadalafil 10 mg alone. Although specific interactions have not been studied, other CYP3A4 inducers, such as carbamazepine, phenytoin, and phenobarbital, would likely decrease tadalafil exposure. No dose adjustment is warranted. The reduced exposure of tadalafil with the coadministration of rifampin or other CYP3A4 inducers can be anticipated to decrease the efficacy of Tadalafil for once daily use; the magnitude of decreased efficacy is unknown. **Potential for Tadalafil to Affect Other Drugs : Aspirin** — Tadalafil did not potentiate the increase in bleeding time caused by aspirin. **Cytochrome P450 Substrates** — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms. Studies have shown that tadalafil does not inhibit or induce P450 isoforms CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. **CYP1A2 (e.g. Theophylline)** — Tadalafil had no significant effect on the pharmacokinetics of theophylline. When tadalafil was administered to subjects taking theophylline, a small augmentation (3 beats per minute) of the increase in heart rate associated with theophylline was observed. **CYP2C9 (e.g. Warfarin)** — Tadalafil had no significant effect on exposure (AUC) to S-warfarin or R-warfarin, nor did tadalafil affect changes in prothrombin time induced by warfarin. **CYP3A4 (e.g. Midazolam or Lovastatin)** — Tadalafil had no significant effect on exposure (AUC) to midazolam or lovastatin. **P-glycoprotein (e.g. Digoxin)** — Coadministration of tadalafil (40 mg once per day) for 10 days did not have a significant effect on the steady-state pharmacokinetics of digoxin (0.25 mg/day) in healthy subjects. **Fertility, pregnancy and lactation: Impairment of Fertility** — There were no effects on fertility, reproductive performance or reproductive organ morphology in male or female rats given oral doses of Tadalafil up to 400 mg/kg/day. **Pregnancy Category B** — Tadalafil is not indicated for use in women. There are no adequate and well controlled studies of Tadalafil use in pregnant women. Based on animal data, Tadalafil is not predicted to increase the risk of adverse developmental abnormalities in humans. **Nursing Mothers** — Tadalafil is not indicated for use in women. Tadalafil and/or its metabolites were secreted into the milk in lactating rats at concentrations approximately 2.4-fold greater than found in the plasma. **Overdose:** Single doses up to 500 mg have been given to healthy subjects, and multiple daily doses up to 100 mg have been given to patients. Adverse events were similar to those seen at lower doses. In cases of overdose, standard supportive measures should be adopted as required. Hemodialysis contributes negligibly to tadalafil elimination.

References:

1. Procial prescribing information
2. Costa P, Grivel T, Gehchan N. Tadalafil I once daily in the management of erectile dysfunction: patient and partner perspectives. Patient Prefer Adherence. 2009;3:105–111.
3. Rubio-Aurioles E, Porst H, Kim ED, et al. A randomized open-label trial with a crossover comparison of sexual self-confidence and other treatment outcomes following tadalafil once a day vs. tadalafil or sildenafil on-demand in men with erectile dysfunction. J Sex Med. 2012;9(5):1418-29.
4. Hatzichristou D, d'Anzeo G, Porst H, et al. Tadalafil 5 mg once daily for the treatment of erectile dysfunction during a 6-month observational study (EDATE): impact of patient characteristics and comorbidities. BMC Urology 2015;15:111.
5. Brock G, Ni X, Oelke M, et al. Efficacy of Continuous Dosing of Tadalafil Once Daily vs Tadalafil On Demand in Clinical Subgroups of Men with Erectile Dysfunction: A Descriptive Comparison Using the Integrated Tadalafil Databases. J Sex Med 2016;13:860e875.
6. Donatucci CF, Wong DG, Giuliano F, et al. Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. Curr Med Res Opin 2008;24:3383-92.
7. Carson CC, Rajfer J, Eardley I, et al. The efficacy and safety of tadalafil: an update. BJU Int. 2004;93(9):1276-81.
8. Porst H, Gacci M, Büttner H, et al. Tadalafil once daily in men with erectile dysfunction: an integrated analysis of data obtained from 1913 patients from six randomized, double-blind, placebo-controlled, clinical studies. Eur Urol. 2014;65(2):455-64.
9. Porst H, Rajfer J, Casabé A, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. J Sex Med 2008;5:2160–2169.

