

Medication Minute

Tadalafil (Cialis[®]) and Vardenafil (Levitra[®]) Recently Approved Drugs For Erectile Dysfunction

Kaye K. Gaines

Erectile dysfunction (ED) affects more than 30 million men in the United States, more than 150 million men worldwide, and accounts for half a million visits to health care providers annually (Sharlip, Jarow, & Rajfer, 2003). In August 2003, the FDA approved vardenafil (Levitra[®] by Bayer/GlaxoSmithKline), and on November 21, 2003, tadalafil (Cialis[®] by Lilly/ICOS) was approved. Both drugs have been available and in widespread use in Europe and Latin America for several months and now join sildenafil (Viagra[®] by Pfizer) as oral treatment options for ED in the United States.

Mechanism of Action

Both tadalafil and vardenafil are (like sildenafil) classified as potent and highly selective phosphodiesterase type 5 (PDE5) inhibitors. Inhibition of PDE5 prevents cyclic guanosine monophosphate (cGMP) from being degraded in penile tissue. When the enzyme is inhibited, relaxation of the smooth muscle in the corpus cavernosum occurs and leads to inflow of blood, potentiating erection. Both drugs require sexual stimulation for response (Palacioz, 2003; Thomson Micromedex, 2003).

Indications/Clinical Studies

Tadalafil and vardenafil are indicated for erectile dysfunction of various etiologies. Both drugs were effective in generalized ED clinical studies and also in studies of special populations of men with diabetes and men post nerve-sparing radical prostatectomy. The ages of men in clinical studies ranged from early 20s to early 80s, with average age being mid-50s. There are no published head-to-head studies of either tadalafil or vardenafil with sildenafil. Most studies have compared the drugs to placebo. Many studies excluded sildenafil nonresponders (Abramowicz, 2003; Broda, 2003; Cialis Prescribing Information, 2003; Levitra Prescribing Information, 2003). In October 2003, results of a 4-week multi-

center, double-blind study of 463 nonresponders to sildenafil were presented at the fall research meeting of the Sexual Medicine Society of North America showing statistical and clinical improvement over baseline in vardenafil users over placebo (Carson et al., 2003).

Dosage/Administration

Tadalafil is available in 10 mg and 20 mg tablets and should be taken orally 30 minutes to 1 hour before sexual activity. Effectiveness may onset in 15 to 30 minutes and can last as long as 36 hours for one dose, facilitating spontaneity. No more than one tablet should be taken in a single 24-hour period. Some clinical trials tested a daily dose of tadalafil (Cialis Prescribing Information, 2003; Porst et al., 2003) (see Patient Education Information, p. 46).

Vardenafil is available in 2.5 mg, 5 mg, 10 mg, and 20 mg tablets. Recommended starting dose for most men is 10 mg taken orally approximately 1 hour before sexual activity. Effectiveness may onset in 30 to 60 minutes and usually lasts approximately 4 to 5 hours (similar to sildenafil). Maximum dosing frequency is once daily (Abramowicz, 2003; Keating & Scott, 2003; Palacioz, 2003; Levitra Prescribing Information, 2003) (see Patient Education Information, p. 46).

Both drugs are well-tolerated and can be taken with or without food, although high-fat meals may delay response time. In mild renal and hepatic impairment, no dose adjustment is required. Dosages may need adjustment in moderate hepatic impairment or in patients receiving potent CYP3A4 inhibitors like ketoconazole, itraconazole, ritonavir, indinivir, and erythromycin (Keating & Scott, 2003; Thomson Micromedex, 2003).

Absorption/Distribution/Metabolism

Vardenafil is metabolized for the most part in the liver, primarily by CYP3A4/5 and to a lesser extent by CYP2C. Mean renal clearance of vardenafil is 2.3 L/hour. It has an elimination half-life of 4 to 5 hours and is excreted mostly (91% to 95%) in feces (Keating & Scott, 2003).

Tadalafil is rapidly absorbed following oral administration, and is also primarily metabolized in

Kaye K. Gaines, MS, RN, CS, CUNP, is a Urology Nurse Practitioner, Bay Pines VA Medical Center, Bay Pines, FL.

the liver by the cytochrome P450 (CYP)3A4 isoform. Mean oral clearance is 2.5 L/hour, and mean half-life is 17.5 hours. Approximately two-thirds of the drug is excreted in the feces, with the other third excreted in the urine (Cialis Prescribing Information, 2003).

Contraindications

- Neither tadalafil nor vardenafil should be taken with nitrates or nitric oxide donors due to the potential for increased hypotensive effect.
- Concomitant use with alpha blockers is also contraindicated due to potential for hypotension.
- Heart attack or stroke within past 6 months, uncontrolled hypertension, significant hypotension, unstable angina, retinitis pigmentosa, severe renal or hepatic impairment are all contraindications for use of PDE5 inhibitors.
- Blood disorders (leukemia, multiple myeloma, sickle cell anemia).
- History of allergy or reaction to sildenafil, tadalafil, or vardenafil.

Precautions

- Increased risk for men with severe cardiac disease due to the vasodilatory effects of PDE5 inhibitors.
- Slightly increased risk of hypotension.
- Rare reports of prolonged erections (>4 hours) or priapism (painful erections >6 hours) have been reported. Permanent tissue damage can occur if untreated in a timely manner.
- PDE5 inhibitors can increase QTc interval. Men at risk for prolonged QT or those taking Class 1A or Class III anti-arrhythmic medications should avoid tadalafil or vardenafil.

Possible Side Effects (most common)

- Headache
 - Flushing
 - Upset stomach/nausea
 - Stuffy nose
 - Urinary tract infection
 - Visual changes such as mild and temporary changes in blue/green colors or increased sensitivity to light (may not be as likely with tadalafil as with vardenafil or sildenafil)
 - Diarrhea
 - Back pain
- (Cialis Prescribing Information, 2003; "FDA Approves," 2003; Levitra Prescribing Information, 2003; Palacios, 2003; Thomson Micromedex, 2003).

Cost

Prices reported in a random survey of local pharmacies ranged between \$8.50 to \$11.50 per tablet for either tadalafil or vardenafil. In most instances, vardenafil's price was slightly higher. There was no difference between prices of 10 mg and 20 mg strengths.

Nursing Considerations

- Verify that patient does not use any form of nitrates (including recreational drugs).
- Observe blood pressure reading prior to initiating treatment.
- Be familiar with drug interactions (drugs that could prolong QT interval, drugs that affect the CYP3A4 pathway, alpha blockers).
- Discuss possible side effects with patients.
- Advise patients of rare possibility of prolonged erection/priapism and need to seek immediate treatment if erection lasts longer than 4 hours.

Conclusion

Sildenafil (Viagra) opened the door and set the bar as the first PDE5 inhibitor for oral treatment of erectile dysfunction and has successfully cornered the market for the past 5 years. The addition of two new PDE5 inhibitors is likely to open new doors for treatment of ED. Vardenafil (Levitra) claims more rapid onset, fewer side effects, and better efficacy overall for some men. Tadalafil (Cialis) makes similar claims and offers the additional benefit of a "weekend pill" (24 to 36 hours duration of action for a single dose). And certainly, apomorphine (Uprima[®]) for sublingual use, apomorphine nasal spray, and alprostadil gel/cream (Topiglan[®]/Alpro-TD[®]) for topical use are probably not far behind in the race to successfully treat a problem that concerns millions of men and their partners and will continue to be a major health issue as baby boomers move into their 50s and beyond. ■

References

- Abramowicz, M. (2003). Vardenafil (Levitra[®]) for erectile dysfunction. *The Medical Letter*, 45(1166), 77-78.
- Broda, C. (2003). Levitra (vardenafil) and Viagra nonresponders. *Pharmacist's Letter*, 19(11), 12.
- Carson, C., Hatzichristou, D., Carrier, S., Lording, D., Young, J., & Murdoch, M. (2003). Vardenafil exhibits efficacy in men with erectile dysfunction unresponsive to prior sildenafil therapy: Results of a phase III clinical trial - patient response with vardenafil in sildenafil nonresponders (PROVEN). Presented at the 5th Annual Fall Research Meeting of the Sexual Medicine Society of North America, October 11, 2003, Denver, CO.
- Cialis Prescribing Information. (2003). Retrieved December 15, 2003, from www.cialisdruginformation.com
- FDA Approves Third Drug to Treat Erectile Dysfunction. (2003). *Pharmacist's Letter*, 19(12), 17.
- Keating, G., & Scott, L. (2003). Vardenafil: A review of its use in erectile dysfunction. *Drugs* 2003, 63(23), 2673-2703.
- Levitra Prescribing Information. (2003). West Haven, CT: Bayer/Glaxo Smith Kline.
- Palacios, K. (2003). New drug: Levitra (vardenafil). *Pharmacist's Letter*, 19(9), 190-901.
- Porst, H., Padma-Nathan, H., Giullano, F., Anglin, G., Varanese, L., & Rosen, R. (2003). Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: A randomized controlled trial. *Urology*, 62(1), 121-126.
- Sharlip, I., Jarow, J., & Rajfer, J. (2003). *The diagnosis and treatment of erectile dysfunction*. Symposium presented April 29, 2003, at American Urological Association 98th Annual Meeting, Chicago, IL.
- Thomson Micromedex. (2003). Tadalafil (Drugdex drug evaluations). Retrieved December 15, 2003, from www.drugdex.com

Patient Education Information

Tadalafil (Cialis®) or Vardenafil (Levitra®)

What Is It?

Vardenafil and tadalafil are both prescription medications taken by mouth for erectile dysfunction (ED) or impotence in men. With sexual stimulation, a man's normal physical response is increased blood flow to the penis, which results in an erection. Both drugs may help to increase blood flow to the penis, and subsequently help with getting and keeping an erection satisfactory for sexual activity.

The drugs are approved for men over the age of 18 years who have ED, including men with diabetes or who have undergone radical prostatectomy.

What It's Not

- Does not protect from sexually transmitted diseases.
- Does not cure erectile dysfunction.
- Is not a means of birth control.
- Does not increase sexual desire.

How and When Is it Used?

- Take exactly as directed by your health care provider.
- Dosage for vardenafil is 2.5 mg, 5 mg, 10 mg, and 20 mg (most common starting dose is 10 mg). One dose of vardenafil may last 2 to 4 hours.
- Dosage for tadalafil is 10 mg or 20 mg. One dose of tadalafil may last as long as 24 to 36 hours.
- May take one dose by mouth approximately 1 hour before planned sexual activity. Sometimes activity of drug may begin within 30 minutes.
- May take one dose every 24 hours as needed. No more than one dose per 24 hours.
- Take medication with or without meals.
- Sexual stimulation is needed in order for erection to occur with either drug.

Who Should Not Take It or Use with Caution?

- Men with heart problems such as angina, heart failure, irregular heartbeat, recent heart attack.
- Low blood pressure or uncontrolled high blood pressure.
- Previous stroke.
- History of rare heart condition "long QT syndrome."
- Liver problems or kidney problems requiring dialysis (dose may need to be adjusted).
- Rare genetic eye disease called retinitis pigmentosa.
- Gastric ulcers.
- History of bleeding problems.
- Past erection that lasted longer than 4 hours (priapism).
- Deformed shape of penis (Peyronies disease).
- Blood disorders (leukemia, multiple myeloma, sickle cell anemia).
- History of allergy or reaction to sildenafil, tadalafil, or vardenafil.

What About Other Medications?

- Do not take with any form of nitrates (medication for angina or chest pain such as nitroglycerin or isosorbide products).
- Do not take with recreational drugs called "poppers" such as amyl nitrate or butyl nitrate.
- Cautious use with alpha blockers [such as terazosin (Hytrin®), doxazosin (Cardura®), tamsulosin (Flomax®), prazosin (Minipress®), and alfuzosin (UroXatral®)] due to possible lowering of blood pressure.
- Do not take with quinidine, procainamide, amiodarone, or sotalol.
- Not to be taken with ritonavir (Norvir®) or indinavir sulfate (Crixivan®).
- Not to be taken with ketoconazole (Nizoral®), itraconazole (Sporonox®), or erythromycin.
- Do not use at same time with other medications for ED.

What Are Possible Side Effects?

- Headaches
- Flushing
- Nasal congestion or runny nose
- Indigestion, nausea, or heartburn
- Dizziness
- Back pain or muscle aches

Less-Common Side Effects

- Visual changes or "blue-green haze."
- Erection that does not go away in at least 4 hours is called priapism. Priapism is considered an emergency since it can cause lasting damage to penile tissue.

Sources

Cialis Drug Information (2003), Levitra Prescribing Information (2003), Thomson Micromedex (2003).

THIS PAGE MAY BE PHOTOCOPIED FOR PATIENT EDUCATION PURPOSES.

Copyright of Urologic Nursing is the property of Society of Urologic Nurses and Associates, Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.