

Safety, Efficacy, and Patient and Partner Acceptability of Vardenafil Orally Disintegrating Tablets for the Treatment of Erectile Dysfunction

Gregory Lowe and John Lavin

Ohio State University Wexner Medical Center, Department of Urology, 915 Olentangy River Rd, Columbus, Oh 43212.
Corresponding author email: gregory.lowe@osumc.edu

Abstract: Staxyn (Bayer HealthCare Pharmaceuticals) is an oro-dispersible form of vardenafil. Oro-dispersible vardenafil functions in the same manner as other phosphodiesterase type 5 inhibitors to prevent the breakdown of cyclic guanosine monophosphate (cGMP), promoting greater erectile response and duration. Pharmacodynamic studies reveal a similar profile to vardenafil 10 mg, with greater bioavailability seen in the oro-dispersible form. Time to maximal concentration is slightly longer with orally dissolving vardenafil, although absorption through the oral mucosa decreases first pass metabolism. Few clinical studies exist on this formulation of vardenafil; however, those available reveal a similar effectiveness to film-coated vardenafil. The POTENT I and POTENT II trials are reviewed and provide the basis for most clinical data on this form of vardenafil. Staxyn has a safety profile comparable to other phosphodiesterase inhibitors, and a similar medication compatibility. Vardenafil ODT's place in erectile dysfunction treatment is currently based largely on patient preference.

Keywords: vardenafil, safety, orally disintegrating, erectile dysfunction, phosphodiesterase inhibitor

Clinical Medicine Reviews in Therapeutics 2013:5 1–10

doi: [10.4137/CMRT.S7349](https://doi.org/10.4137/CMRT.S7349)

This article is available from <http://www.la-press.com>.

© Libertas Academica Ltd.



Introduction

In medicine, many medications are available in different formulations to provide alternative pharmacokinetics or meet patient preferences. Antibiotics are available in a liquid or pill form to meet the needed dose and assist children in compliance with the medication. Testosterone preparations are available in oral, patch, topical gel, injection and buccal forms, providing patients with an opportunity to choose the option that is most suitable. Until recently, there were no alternative formulations for phosphodiesterase type 5 inhibitors (PDE5i). Staxyn (Bayer HealthCare Pharmaceuticals) is an oro-dispersible form of vardenafil. The new formulation of vardenafil hydrochloride was approved by the FDA on June 17th, 2010. Staxyn was approved at a dose of 10 mg on demand and requires a prescription for purchase.

Original formulations of PDE5i are film-coated tablets achieving high selectivity for phosphodiesterase type 5. The absolute bioavailability is only 15% due to first pass hepatic metabolism in film-coated forms.¹ In the authors' experience, some men prefer an alternative formula of PDE5i to allow a more discrete option for taking the medication when not at home or with a new partner. The idea that some men may prefer an alternative formulation is further confirmed through a Google internet search for "vardenafil online pharmacy" revealing several formulations of PDE5i being sold that are not approved by the United States Food and Drug Administration (FDA). Such formulations offered include soft tablets, chewable tablets, or oral jelly.

Oro-dispersible (ODT) is a form of medication administration providing rapid disintegration in the mouth. This is also known as mouth dissolving or rapid dissolving forms. The ODT form entered the market in the 1980s as an attempt to improve patient compliance and acceptability for particular medications.² It offered patients with difficulty swallowing or nausea an alternative to liquid or traditional tablet formulations. These medications can also avoid first pass metabolism if they can be absorbed through the oral mucosa.

This review covers the available data on Staxyn after two years of clinical availability. A literature review was performed on the PubMed website (<http://www.pubmed.com>) using the search terms "vardenafil", "orodispersible", "Staxyn", "rapid dissolving and

vardenafil", "mouth dissolving and vardenafil", "orally disintegrating", and "POTENT and vardenafil". Available articles were reviewed and the references were further evaluated for additional resources. A review of recent program abstracts from the Sexual Medicine Society of North America was performed, searching for Staxyn and orally disintegrating vardenafil. Finally, the authors' own patient experiences and a review of FDA data are incorporated.

Mechanism of action

Currently, all available forms of PDE5i provide a similar physiologic response. During sexual stimulation, parasympathetic neural activity leads to an increase in blood flow into the cavernous sinuses and smooth muscle relaxation. Nitric oxide is released from the endothelium and leads to increases in intracellular cyclic guanosine monophosphate (cGMP). Through a cGMP-dependant protein kinase, there is a decrease in intracellular calcium concentration and relaxation of the smooth muscle. Penile sinusoid filling follows smooth muscle relaxation and results in compression of the subtunical venous plexus. Blood is trapped within the corpus cavernosum, raising the penis to an erect position. PDE5i prevents the breakdown of cGMP, thereby promoting greater erectile response and duration.

Oro-dispersible vardenafil functions in the same manner as film-coated vardenafil. Sexual stimulation is required to initiate the neural response. Following initiation of the erectile response, vardenafil blocks phosphodiesterase type 5 (PDE5) from breakdown of cGMP. Phosphodiesterase type 5 is the most abundant phosphodiesterase in the penis. Other phosphodiesterase forms exist throughout the body and can be affected by vardenafil in both film coated and oro-dispersible forms. Vardenafil is more selective for PDE5 than all other phosphodiesterases, a fact exploited to limit side effects.⁴

Metabolism

Vardenafil is metabolized predominantly by hepatic reduction-oxidation. This primarily occurs through the CYP3A4 cytochrome P450 enzyme. CYP3A5 and CYP2C9 isoforms provide additional breakdown contributions.¹ The demethylation of the piperazine moiety of vardenafil creates the major metabolite, designated M-1.⁴ M-1 has a similar PDE5 selectivity as



the parent compound, but has a decreased inhibitory potency of 28%. M-1 plasma concentration reaches 26% of the concentration for vardenafil. Overall, the M-1 compound contributes 7% of the total activity from a single dose of vardenafil.⁵

The half-life of ODT vardenafil 10 mg was measured at between 4.2 to 6 hours, similar to the film-coated form (10 mg) half-life of 4.5 to 6.2 hours.¹ The 20 mg film-coated form has been described as having a half-life of 3.9 hours.⁵ The M-1 half-life was 2.5 to 3.2 hours in the ODT formulation. Again, this is similar to the 2.2 to 3.5 M-1 half-life of the film-coated vardenafil. There was little difference in ODT vardenafil half-life if the dosing was single, or after multiple days of dosing.¹ An absolute difference in half-life was noted between patients older and younger than 65 years. Those older than 65 years experienced a half-life of 6 hours compared to a half-life of 4.4 hours in younger subjects following a 10 mg dose of ODT vardenafil. Up to 95% of an oral dose of vardenafil is excreted in the feces, with a smaller portion excreted in the urine.

Pharmacokinetic properties

Three clinical studies have been performed to assess pharmacokinetic properties of Staxyn.¹ Each study involved dosing of the 10 mg ODT vardenafil, followed by frequent blood sample evaluation for plasma levels of vardenafil and the M-1 metabolite. Study 12769 evaluated 13 healthy men aged 18–50 years and focused on the effect of food and drink on absorption. The men each participated in one of four scenarios over a 6-week time frame. Three scenarios involved ODT and one involved 10 mg of film-coated vardenafil. Study 13396 utilized subjects over 18 years of age and with a history of erectile dysfunction for at least 6 months. Twenty subjects were younger than 65 years and 14 subjects were older than 65 years of age. This study evaluated the role of once-daily dosing of Staxyn 10 mg for 10 straight days. Study 12093 was a phase III multicentre study comparing Staxyn 10 mg with placebo in a group of men with greater than 6 months of erectile dysfunction. Twenty-five subjects underwent pharmacokinetic evaluation at the end of the study. A 48-hour washout was utilized prior to a vardenafil ODT 10 mg dose without water.

A total of 72 subjects were available for analysis. Mean BMI ranged from 25.7 kg/m² to 29.4 kg/m² for

the three studies. The majority of individuals were Caucasian. Twenty-seven of the men were 65 years of age or older.

Absorption

Vardenafil ODT 10 mg and film-coated 10 mg forms both became detectable 20 minutes after dosing. Interestingly, the vardenafil ODT lagged behind the film-coated formulation by about five to ten minutes to become measurable. The early systemic concentrations largely overlapped. The ODT formulation disintegrates on the tongue rapidly, in approximately 9 seconds.

Maximum concentration

Vardenafil in the film-coated formulation reached a higher plasma vardenafil maximum concentration; however, this only reached significance in men greater than 65 years of age. Vardenafil ODT reached 81% (90% CI: 67–98%) of the maximum concentration seen in the film-coated formulation for men over 65 years of age. For men younger than 65 years, the 90% confidence interval overlapped between men utilizing the ODT and film-coated formulations. The absolute value in these subjects favored the film-coated formulation.

Time

Vardenafil in the film-coated formulation had a median time to max concentration (T_{max}) of 0.75 hours (ranging from 0.5 to 3 hours) regardless of patient age. For men younger than 65 years, the median T_{max} was 1.25 hours (ranging from 0.75 to 2.5 hours). Men older than 65 years had a lower T_{max} of 0.875 hours (range 0.5 to 3 hours). The T_{max} remained stable when comparing an isolated single dose and at the end of the 10 day dosing. The half-life of vardenafil was shown to be independent of formulation.

Bioavailability

Although the film-coated formulation tended to reach a higher maximum concentration, the bioavailability is greater for the ODT formulation. After reaching maximum concentration, the film-coated plasma concentration showed a more rapid decline compared with the ODT form. The plasma concentration of vardenafil ODT was higher at one hour and remained higher for several hours. Overall, the ODT form



showed 27% higher bioavailability over film-coated dosing in patients younger than 65 years with erectile dysfunction. Healthy young men had a 44% higher bioavailability. For men older than 65 years, the ODT form was associated with 21% higher bioavailability.

Effects of diet

The role of food and water was assessed in healthy volunteers in study 12769. The bioavailability and T_{max} were not significantly different in the fed state when compared with fasting. In the fed scenario, the maximum concentration was decreased by 35%. Taking the ODT formulation with water decreased the bioavailability by 29% when compared to taking the ODT formulation without water. When taken with water, the ODT formulation paralleled the bioavailability of the film coated vardenafil. Taking the ODT form with water did not increase the maximum concentration over that seen with film-coated vardenafil; however this did decrease the T_{max} of the ODT formulation to 0.5 hours. Prior studies have shown that if a film-coated vardenafil is held in the mouth, there is a small amount of oral mucosal absorption and delayed T_{max} . The amount of vardenafil absorbed through the oral mucosa appears to be similar when comparing an ODT with a film-coated formula.¹ Therefore, taking the ODT form with water relegates it to perform similarly to the film-coated vardenafil, with shortened time to maximum concentration but lower overall bioavailability. In summary, the ODT formulation of vardenafil should not be taken with water, but is not altered by food intake.

Hepatic and renal impairment

Vardenafil ODT has not been specifically evaluated in these patient populations. Given the overlap in pharmacokinetic parameters, the packaging insert has provided vardenafil film-coated data.⁴ Mild hepatic impairment showed an increase in both bioavailability and maximum concentration. Moderate hepatic impairment (Child-Pugh B) demonstrated an increased bioavailability of 160% for the 10 mg dose. Severe hepatic dysfunction has not been specifically evaluated. These findings are not surprising based on the metabolism of vardenafil. Renal dysfunction has been evaluated as well. No difference in bioavailability was noted until creatinine clearance values were lower than 50 mL/min. In patients with impaired

creatinine clearance, the bioavailability increased by 20%–30%. Dialysis dependant patients have not been specifically evaluated.

Clinical studies

PDE5i remain first line therapy for erectile dysfunction according to the American Urologic Association guideline on erectile dysfunction, unless contraindications exist.³ There have been two phase III studies published on vardenafil ODT, with several subsequent publications analyzing this data further. The two trials were named POTENT I and POTENT II based on the title “Pivotal phase III trial to investigate the efficacy and safety of an orodispersible tablet vardenafil versus placebo in the treatment of men with erectile dysfunction: a fixed-dose, double-blind, randomized, multi-center trial”.^{6,7} Unique to POTENT trials (compared to film coated PDE5i trials) was the effort to evaluate men over the age of 65 years, with approximately 50% of patients above this age.

Methods were similar between the two POTENT trials. Blinding continued until the end of the studies. Men were included if they had erectile dysfunction for greater than 6 months, as defined by the National Institutes of Health Consensus Panel on Impotence. Patients also had to be in a stable heterosexual relationship over the previous 6 months having attempted sexual activity on at least 4 separate days with at least half of attempts unsuccessful, and be interested in treatment for erectile dysfunction. Patients were excluded if they had: severe cardiovascular disorder within 6 months, prior prostatectomy, spinal cord injury, medications contraindicated for use with vardenafil or phenylketonuria. Both studies consisted of a four-week run-in period without medication followed by a 12-week treatment phase. Study medication could be taken once a day. Patients were randomized to receive placebo or vardenafil ODT 10 mg, with both groups educated to place the medication on the tongue without water. Food intake was left to patient preference. Patients were educated to wait one hour prior to attempted sexual activity. Safety data were collected 48 hours after ingestion of the last dose of study medication via a physician visit or telephone call. The groups were stratified to allow 50% of subjects to be greater than 65 years of age. Data was analyzed with intent-to-treat and in a per-protocol fashion.



Data collected for efficacy included the erectile function domain of the International Index of Erectile Function (IIEF-EF), Sexual Encounter Profile question 2 (SEP2: Were you able to insert your penis into your partner's vagina) and Sexual Encounter Profile question 3 (SEP3: Did your erection last long enough for you to have successful intercourse). These were each collected at baseline, after a 4-week non-medicated run-in, and following the treatment phase. Secondary information obtained included all other Sexual Encounter Profile questions, the Treatment Satisfaction Scale for patients, the Global Assessment Question ("Has the treatment you have been taking over the past four weeks improved your erections? Please compare to your erections prior to participation in this study"), and an evaluation of the number of patients returning to an IIEF-EF score ≥ 26 .

Safety data included reporting of all adverse events, hematologic and urine laboratory analysis, vital signs, physical examination and electrocardiography at the start of the study and at the last visit.

POTENT I included men from 40 medical centers in France, Germany, Spain, Belgium, South Africa, and the Netherlands.⁶ POTENT II included men recruited at 35 medical facilities from Australia, United States, Mexico and Canada.⁷ As phase III studies, both were funded by Bayer Schering Pharma and investigators from the company provided support in the study.

Other unique clinical studies have not been published. An integrated analysis has been performed combining the data from POTENT I and POTENT II.⁸ Additionally, there has been a retrospective analysis of these two trials and several studies on film-coated vardenafil specifically looking at time-to-onset of efficacy.⁹

Clinical efficacy

POTENT I

Of the 362 men randomized, 355 men comprised the intent-to-treat population. Thirty-two patients discontinued treatment early, 13 of which were in the vardenafil ODT group. Results were similar between the intent-to-treat and per-protocol populations. At baseline, a mean IIEF-EF score of 12.9 indicated moderate erectile dysfunction in both the placebo and treatment groups. After 12 weeks of treatment, the mean IIEF-EF score was 21.5 in the vardenafil

ODT group compared to 14.4 in the placebo patients ($P < 0.0001$). SEP2 was successful for 73.7% of treatment patients compared to 46.7% of placebo patients ($P < 0.0001$) and this had increased from 40.4% and 38.8% at baseline, respectively. SEP3 showed significant improvement in the treatment group from 13.6% to 64.9%. This increase was significantly greater than the improvement seen in the placebo group (15.2% to 26.7%, $P < 0.0001$). The percentage of patients reporting return-to-normal erectile function (IIEF-EF ≥ 26) was 40% for vardenafil ODT and only 12% for placebo (Table 1). The Global Assessment Question was positive for 72% of treatment patients and 26% of placebo patients ($P < 0.0001$).

POTENT II

In the POTENT II trial, 339 men were randomized and 331 comprised the intent-to-treat population. Forty-four patients discontinued treatment early, approximately half from the vardenafil ODT group. The mean IIEF-EF score for patients in the placebo group was 12.8 at baseline and increased to 13.9 after 12 weeks of treatment. Mean IIEF-EF score at baseline was 11.7 and increased to 20.8 after 12 weeks of treatment in the vardenafil ODT group. The increase was statistically greater in the vardenafil treatment group compared to the placebo group ($P < 0.0001$). Success as defined on SEP2 was greater among treatment patients after 12 weeks compared with placebo (69% versus 43%, $P < 0.0001$). Baseline SEP2 scores were similar between vardenafil treatment (36.4%) and placebo (38.3%) patients. SEP3 success was greater among treatment patients as well. Vardenafil ODT patients increased SEP3 success from 12.5% at baseline to 60%. This improvement was statistically significantly

Table 1. Percent success in primary and secondary end points following a 12-week treatment protocol.

	SEP3 success (%)	Global Assessment Question success (%)	IIEF-EF ≥ 26 (%)
Placebo			
POTENT I	26.7	26	12
POTENT II	26.6	24	9
Vardenafil ODT			
POTENT I	64.9	72	40
POTENT II	60	67	46



improved ($P < 0.0001$) over that observed in the placebo group (15.2% to 26.6%). Return-to-normal erectile function was 46% in the vardenafil ODT group compared with 9% in the placebo group. 67% of the vardenafil group and only 24% of the placebo group responded favorably to the Global Assessment Question ($P < 0.0001$).

Integrated analysis

The integrated analysis performed by Sperling and colleagues⁸ provided an assessment of both POTENT I and POTENT II in men aged 65 years and older and in men with specific medical conditions. Baseline characteristics noted a higher incidence of cardiovascular disease, dyslipidemia and hypertension in men 65 years and older. In this population of older men, approximately half were diagnosed with hypertension and at least a quarter had diabetes. Half of men at least 65 years were present or past smokers and 50% had previously expressed satisfaction with PDE5i therapy. Overall, 360 men older than 65 years were randomized to participate with 176 in the placebo arm and 184 receiving treatment with vardenafil ODT 10 mg. Men 65 years and older had numerically lower IIEF-EF scores, SEP2 success and SEP3 success at baseline and after treatment regardless of receiving placebo or vardenafil ODT when compared with younger men. Regarding men greater than 65 years old, the mean IIEF-EF increased to 19.6 in the treatment group and was not significantly different from the improvement noted in men younger than 65 years. After 12 weeks of treatment, men 65 years of age and older showed higher success among men in vardenafil ODT compared with placebo groups for both SEP2 (66.9% versus 42.2% respectively) and SEP3 (56.9% versus 22.5%). These improvements in the treatment arm were not statistically different from that seen in men younger than 65 years for SEP2 and SEP3.

Men with underlying medical conditions (regardless of age) showed significant improvement after receiving vardenafil ODT compared with placebo. This improvement was not significantly different compared to the improvement seen in men without underlying conditions ($P > 0.05$ for all measures). The findings of vardenafil ODT efficacy from this study are in agreement with a meta-analysis of studies evaluating film-coated vardenafil.¹⁰ The film-coated vardenafil

also revealed efficacy regardless of age or underlying medical conditions.

Time-to-onset

Retrospective analysis of POTENT I and POTENT II data has been analyzed and compared with similar phase III clinical trials for vardenafil film-coated 10 or 20 mg doses.⁹ This analysis was conducted to determine if time to onset of medication activity was different between the film-coated and ODT forms of vardenafil. Patients were asked to complete a diary within 24 hours of each sexual attempt to assess when medication was taken, time of initiation of sexual activity and success at particular time points. SEP3 was used to define success for this study. Not all patients attempted sexual activity at these early time points, and therefore success at each time reflects analyses of patients who did attempt sexual activity.

For vardenafil ODT, overall 59.8% of attempts at 15 minutes were successful and this reached a 75.7% success rate at 30–45 minutes. The placebo group showed 38.2% success at 15 minutes and peaked at 51% at 15–30 minutes. Assessing all attempts in the first 60 minutes, patients with vardenafil ODT treatment were 64.1% successful compared to 36.2% for the placebo group. The film-coated form of vardenafil revealed similar SEP3 success results for all time points evaluated. Care should be taken when considering this data, however, as the studies were not specifically designed to assess time as an end-point, and results were based on patient recall. Fewer attempts were undertaken at shorter time points, potentially influencing the success percentage. The data does suggest that clinically significant plasma levels of vardenafil are achieved prior to reaching the maximum concentration.

Alternative end-points

Vardenafil ODT has not been evaluated for alternative end-points besides those listed above. Vardenafil as a film-coated form has been evaluated specifically for female partner satisfaction and in men with lifelong premature ejaculation.^{11,12} Female partners were at least 18 years of age with no significant sexual dysfunction and only the male partner took vardenafil.¹¹ The modified Sexual Life Quality Questionnaire (mSLQQ-QOL) assessed the female partner's sexual quality of life. The baseline score on mSLQQ-QOL was 28.8 and



24.6 in the treatment and placebo groups, respectively. This value increased to 68.2 in the treatment group and was significantly higher than the increase to 40.5 in the placebo group. All individual items in the 10-question evaluation showed significant improvement to levels near those seen prior to the onset of male partner erectile dysfunction. This improvement in female partners was similar to the improvement seen in men for the same questionnaire.

In a double-blind laboratory study of men with lifelong premature ejaculation, evaluation was performed with audio-visual sexual stimulation followed by application of penile vibratory stimulation to the penile frenulum.¹² Once reaching ejaculation, the ejaculation latency time was recorded. Subjects were divided into four groups including placebo, 10 mg vardenafil, 50 mg sildenafil, or 20 mg tadalafil. The results showed that only vardenafil ejaculatory latency time (82.5 seconds) was significantly different from placebo (48.5 seconds).

Safety

The similar pharmacokinetic and clinical properties of vardenafil ODT to film-coated vardenafil suggest a common safety profile. The safety data specific to vardenafil ODT was documented in the POTENT I and POTENT II trials. Safety was determined by assessing for adverse events at all visits and 48 hours after the final medication dose. All randomized patients taking at least one dose of the study medication and with one follow-up were included in the safety analysis (N = 695). Prior to assessing this data, it is important to determine the characteristics of patients assessed.

The patient characteristics for those in the safety assessments were documented in the combined integrated analysis.⁸ For patients less than 65 years of age, cardiac disorders were noted in 15.2% and 6.9% of placebo and vardenafil ODT patients respectively. The younger patient group had documented diabetes in 24% of both placebo and treatment groups, dyslipidemia in at least 28% and hypertension in at least 30%. Patients over 65 years tended to show a greater percentage of underlying conditions. Older patients had approximately 49% hypertension and at least a 25% rate of diabetes in treatment and placebo subjects. Only one patient in the placebo arm and seven in the vardenafil ODT arm prematurely discontinued the study due to an adverse event.

A higher incidence of treatment-emergent adverse events was seen in the vardenafil ODT group, with 38% of patients experiencing an event, compared to the placebo group. Events deemed drug related were also higher in the vardenafil ODT arm, with 24.2% of events classified as drug related compared with 7.4% of those in the placebo group. Serious adverse events (including chest pain, acute coronary syndrome, and hypertension) were seen in less than 1% of patients in the vardenafil treatment group and not all were deemed related to the study medication. No deaths were observed. Patients less than 65 years of age had a higher incidence of treatment-emergent and drug-related adverse events than those older than 65 years in the vardenafil group.

Specific adverse events are of particular concern for patient safety, including cardiac arrhythmia, dizziness and oral irritation. Prior research has shown vardenafil to be safe based on FDA post-marketing data.¹³ Cardiovascular adverse events were reported in 5% of the vardenafil patients. Limitations of this data exist but it does provide a true population-based analysis. Subjects from the POTENT I and POTENT II trials are more closely related to this patient population than the prior PDE5i phase III trials due to the increased number of patients greater than 65 years of age. Overall, the POTENT trials showed that only four of 355 vardenafil treatment patients had cardiac arrhythmias. Dizziness was observed in 1.6% of older and 2.9% of younger patients. Vasodilation, headache, facial flushing and nasal congestion were the most commonly seen adverse events, regardless of age. Back pain was seen in just over 1% of vardenafil ODT patients.

Similar to other PDE5i, vardenafil ODT should be used with caution in patients taking CYP3A4 inhibitor medications. These medications include clarithromycin, atazanavir, indinavir, ritonavir, itraconazole, ketoconazole and erythromycin. Nitrates are a contraindication to use of vardenafil ODT and care should be taken when initiating alpha-blocker therapy at the same time as vardenafil. Unique to vardenafil ODT is a safety concern for patients with fructose intolerance or phenylketonuria patients. Staxyn contains a small amount of sorbitol and phenylalanine.

Recent reviews have documented unusual adverse events with all PDE5i medication however these are not clear regarding causality.¹⁴ These unusual events include neurological disorders, sensory disturbances, and case reports of cholestatic hepatotoxicity or



venous thromboembolism. Animal and human studies have suggested a risk of seizures, migraines and abnormal electroencephalographic changes. It has been proposed that the neural toxicity is a result of changes in blood oxygen tension and PDE5i-induced alteration in the vasoconstrictive cerebrovascular response.¹⁴ Additionally, the vardenafil package insert notes a risk of somnolence, syncope, amnesia, and paresthesia from prior vardenafil film-coated studies.⁴ Visual changes remain a concern with any PDE5i therapy. Nonarteritic ischemic optic neuritis leading to irreversible blindness has been reported. Ototoxicity with hearing loss has been reported and is suspected to be secondary to congestion causing Eustachian tube changes or direct effects of phosphodiesterase inhibition in the middle ear. Other rare PDE5i events include ocular hyperemia, eye pain, tinnitus, vertigo, skin rash, and priapism.⁴

Safety data appears to be similar to that of the film-coated vardenafil and therefore the same precautions should be extended to vardenafil ODT.

Patient preference

No specific study has addressed the preference for vardenafil ODT compared to film coated PDE5i. Several factors have been proposed as key determinants for patient preference.¹⁵ These include patient factors of age, frequency of sexual activity, relationship dynamics and duration of erectile difficulties. Partner factors contribute as well and include interest in sex, age and abstinence time from sexual activity. Efficacy and consistency of response are strong determinants of a particular medication but other aspects of the medication also contribute to the preference patterns. Time-to-onset, duration of action and adverse events are important factors. Cost and insurance coverage may determine the preferred medication. Finally, with vardenafil ODT, the route of administration is another variable for patients to consider when determining preferred medication.

Currently available studies documenting preference for one PDE5i over another have limitations in study design. No ideal study directly comparing forms of PDE5i exists. Often there is no blinding involved and patients are aware of the particular instructions and limitations of each medication. Studies may be sponsored by the manufacturer and therefore are criticized due to potential biases of the funding source.

One prospective, open-label, crossover, randomized study evaluated patient preference for all three film-coated forms of PDE5i.¹⁶ Each was taken at the maximal recommended dose. Each showed a significant increase in IIEF scores. Twenty per cent of patients preferred vardenafil in this study, with 28% preferring sildenafil and 52% preferring tadalafil. The limitations of this study include the small patient population and non-blinded approach, with patients receiving differing counseling for each drug.

A larger, double-blind, non-inferiority study found a 39% preference for vardenafil compared with a 35% preference for sildenafil.¹⁷ In this study, 26% of patients had no preference. Another large observational study found high therapeutic effectiveness for all three forms of PDE5i and a slightly higher level of patient satisfaction among patients taking tadalafil.¹⁸ This study did not specifically address patients attempting more than one PDE5i and relied on the non-comparative reported satisfaction with selected PDE5i. A 2007 study evaluating patient compliance found that 25% of patients changed their preferred PDE5i medication over a 3-year period.¹⁹

Reviews evaluating patient preference for film-coated PDE5i have consistently determined that the study results are inconclusive and limited by bias.^{20,21}

Place in therapy

No specific study has evaluated the place in therapy for vardenafil ODT. Staxyn has been marketed as an alternative approach to PDE5i medication. It has been given a peppermint flavor and placed in a dis-

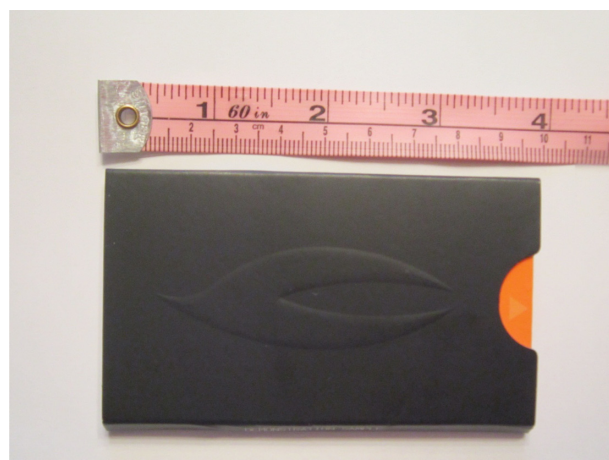


Figure 1. Vardenafil ODT (Staxyn) packaging discretely resembles mint or gum packs.



Figure 2. Vardenafil ODT (Staxyn) foil wrapped medication pockets can be seen extended out from the main cover.

crete package resembling a package of gum (Fig. 1). Additionally, the medication is foil-wrapped to prevent moisture and medication dissolving (Fig. 2). Anecdotally, men have commented that they feel more comfortable taking this medication at dinner, without feeling the need to hide the medication. Ultimately, the orodispersible vardenafil offers patients an alternate option but does not dramatically differ from film-coated varieties.

Conclusion

Vardenafil ODT is a peppermint-flavored, orally disintegrating PDE5i with pharmacodynamic properties similar to vardenafil film coated forms. The packaging promotes a more discrete presentation, and since the medication does not require water consumption, patients are not limited as to when the medication can be used. The effectiveness appears to be equal to film-coated vardenafil and is not affected by food. Vardenafil ODT does require the same safety and medication contraindications seen with the other PDE5i. This unique medication option provides patients with an alternative to the traditional PDE5i.

Author Contributions

Conceived and designed the experiments: GL. Analyzed the data: GL. Wrote the first draft of the manuscript: GL. Contributed to the writing of the manuscript: GL, JL. Agree with manuscript results and conclusions: GL, JL. Jointly developed the structure and arguments for the paper: GL. Made critical

revisions and approved final version: GL. All authors reviewed and approved of the final manuscript.

Funding

Author(s) disclose no funding sources.

Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

References

1. Heinig R, Weimann B, Dietrich H, Bottcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. *Clin Drug Investig.* 2011;31(1):27–41.
2. Green R, Hicks R. Orally disintegrating vardenafil tablets for the treatment of erectile dysfunction: efficacy, safety, and patient acceptability. *Patient Prefer Adherence.* 2011;5:181–5.
3. Montague D, Jarow J, Broderick G, et al. The management of erectile dysfunction: An update. American Urological Association Education and Research, Inc, 2011; Available at <http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/main-reports/edmgmt/content.pdf>.
4. Staxyn (vardenafil hydrochloride) package insert, revision date 2010.
5. Bischoff E. Vardenafil preclinical trial data: potency, pharmacodynamics, pharmacokinetics, and adverse events. *Int J Impot Res.* 2004;16(Suppl 1): S34–7.
6. Sperling H, Debruyne F, Boermans A, Beneke M, Ulbrich E, Ewald S. The POTENT I randomized trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *J Sex Med.* 2010;7(4 Pt 1):1497–507.
7. Gittelman M, McMahon C, Rodriguez-Rivera JA, Beneke M, Ulbrich E, Ewald S. The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *Int J Clin Pract.* 2010;64(5):594–603.
8. Sperling H, Gittelman M, Norenberg C, Ulbrich E, Ewald S. Efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction in elderly men and those with underlying conditions: an integrated analysis of two pivotal trials. *J Sex Med.* 2011;8(1):261–71.



9. Debruyne FM, Gittelman M, Sperling H, Borner M, Beneke M. Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. *J Sex Med.* 2011; 8(10):2912–23.
10. Eardley I, Lee JC, Shabsigh R, et al. Vardenafil improves erectile function in men with erectile dysfunction and associated underlying conditions, irrespective of the use of concomitant medications. *J Sex Med.* 2010;7(1 Pt 1): 244–55.
11. Martin-Morales A, Graziottin A, Jaoude GB, et al. Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: A randomized, double-blind, placebo-controlled study. *J Sex Med.* 2011;8(10):2831–40.
12. Gokce A, Halis F, Demirtas A, Ekmekcioglu O. The effects of three phosphodiesterase type 5 inhibitors on ejaculation latency time in lifelong premature ejaculators: a double-blind laboratory setting study. *BJU Int.* 2010;107(8): 1274–7.
13. Lowe G, Costabile RA. 10-year analysis of adverse event reports to the Food and Drug Administration for phosphodiesterase type-5 inhibitors. *J Sex Med.* 2012;9(1):265–70.
14. Shindel AW. 2009 update on phosphodiesterase type 5 inhibitor therapy part 2: updates on optimal utilization for sexual concerns and rare toxicities in this class. *J Sex Med.* 2009;6:2352–64.
15. Mulhall JP. Understanding erectile dysfunction medication preference studies. *Curr Opin Urol.* 2004;14(6):367–73.
16. Tolra JR, Campana JM, Ciutat LF, Miranda EF. Prospective, randomized, open-label, fixed-dose, crossover study to establish preference of patients with erectile dysfunction after taking the three PDE-5 inhibitors. *J Sex Med.* 2006;3(5):901–9.
17. Rubio-Aurioles E, Porst H, Eardley I, Goldstein I. Comparing vardenafil and sildenafil in the treatment of men with erectile dysfunction and risk factors for cardiovascular disease: a randomized, double-blind, pooled crossover study. *J Sex Med.* 2006;3(6):1037–49.
18. Marin-Morales A, Haro JM, Beardsworth A, et al. Therapeutic effectiveness and patient satisfaction after 6 months of treatment with tadalafil, sildenafil, and vardenafil: results from the erectile dysfunction observational study (EDOS). *Eur Urol.* 2007;51(2):541–50.
19. Ljunggren C, Hedelin H, Salomonsson K, Stroberg P. Giving patients with erectile dysfunction the opportunity to try all three available phosphodiesterase type 5 inhibitors contributes to better long-term treatment compliance. *J Sex Med.* 2008;5(2):469–75.
20. Martin-Morales A, Casillas M, Turbi C. Patients' preference in the treatment of erectile dysfunction: a critical review of the literature. *Int J Impot Res.* 2011;23(1):1–8.
21. Al-Shaiji TF, Brock GB. Phosphodiesterase type 5 inhibitors for the management of erectile dysfunction: preference and adherence to treatment. *Curr Pharm Des.* 2009;15(30):3486–95.