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QNASL® (BECLOMETHASONE DIPROPRIONATE)

Travis Allen, Pharm.D. Candidate

Allergic rhinitis is an IgE-antibody mediated inflammation of the nasal airways resulting in symptoms of sneezing, nasal obstruction, and mucous discharge.[1] Allergic rhinitis, the most common type of non-infectious rhinitis, affects 20-40 million individuals in the US each year.[2] The subtypes of allergic rhinitis include seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and mixed seasonal/perennial allergic rhinitis. The incidence of each subtype has been estimated at 20%, 40%, and 40%, respectively.[2]

Many treatment options exist for allergic rhinitis including antihistamines, decongestants, corticosteroids, leukotriene modifiers, and cromolyn. Intranasal medications are often the cornerstone of therapy with intranasal corticosteroids (INS) having the most efficacy.[3] Currently, INSs approved for allergic rhinitis are manufactured as an aqueous pressurized metered dose inhaler (pMDI). Disadvantages of pMDIs include the need for surfactants and lubricants, which allow for proper function of the inhaler, but can also lead to problems with patient adherence. Patients with aqueous nasal sprays report that taste, post nasal medication drip, and nose run out are the three most common complaints surrounding medication administration.[4,5]

Beclomethasone dipropionate has been used for decades to treat allergic rhinitis; however, in March 2012 TEVA pharmaceuticals received FDA approval for Qnasl®, a new non-aqueous or "dry" nasal spray form of beclomethasone dipropionate. Qnasl® is indicated for the treatment of nasal symptoms associated with SAR and PAR in adults and adolescents 12 years of age and older.[6]

This article will review the new nasal aerosol dosage form of beclomethasone dipropionate including its pharmacology, pharmacokinetics, efficacy, safety, and dosing.

Pharmacology

Beclomethasone dipropionate (BDP) is a corticosteroid prodrug with anti-inflammatory effects. Upon nasal inhalation, BDP is cleaved into the active metabolite, beclomethasone-17-monopropionate (BMP). BMP, in vitro, has affinity for the glucocorticoid receptor 25 times that of BDP, 13 times that of dexamethasone, 6 times that of triamcinolone acetonide, and 1.5 times that of budesonide.[6] While the exact mechanism is unknown, it is believed that BDP and other corticosteroids reduce allergic rhinitis symptoms by inhibiting inflammatory cells and suppressing the release of inflammatory mediators.[7]

Despite a lack of evidence for corticosteroid's mechanism of action, several studies have indicated that BDP reduces nasal airway hyper-responsiveness after antigen exposure. The use of BDP twice daily for seven

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days led to a reduction in early mediator inflammatory response as well as a 24hr sustained reduction in eosinophil count.[8]

Pharmacokinetics

After intranasal administration, BDP is rapidly metabolized into its active form, BMP. The bioavailability of intranasal BDP is 27% when compared to the inhalation dosage form (**Table 1**).[6] The elimination half-life of BMP is 4.5 hours.[6]

BDP is metabolized by the cytochrome P450 system (CYP), namely the CYP3A4 pathway, which produces two inactive metabolites in addition to the active BMP.[9] The metabolites of BDP are mainly eliminated via the fecal route with less than 10% undergoing renal elimination.[6] The pharmacokinetic profile of BDP combined with its local administration contributes to a relatively low risk for clinically significant drug interactions. No dose adjustments are warranted if intranasal BDP is used with other CYP3A4 substrates.[6]

Clinical Trials

Intranasal dry beclomethasone dipropionate (Qnasl®) was approved by the FDA based on three randomized, double blind, placebo controlled trials enrolling a total of 1,049 patients (**Table 2 and 3**).[6,10,11] In addition, a 52 week safety trial and an efficacy trial in patients 6-11 years with SAR were conducted (**Table 2 and 3**).[12,13]

Dose Ranging Trial

The dose ranging trial was a two week trial evaluating the efficacy of three doses of aerosolized BDP (80, 160, and 320 mcg totally daily dose), administered as two sprays in each nostril in patients with SAR.[6] The trial enrolled a total of 244 patients, monitoring them for two weeks to assess the average AM and PM patient reported reflective Total Nasal Symptom Score (rTNSS). At the conclusion of the trial, only the 320 mcg daily dose demonstrated statistically significant improvements in nasal symptoms (rTNSS) compared with placebo (p=0.013). The 320 mcg daily dose also resulted in a statistically significant decrease in morning instantaneous Total Nasal Symptom Scores (iTNSS) compared to the placebo arm, demonstrating that the effect of the intervention was sustained over the 24 hour dosing period.[6]

Table 1 | Pharmacokinetic Properties of beclomethasone dipropionate 320 mcg [6,9,16]

Pharmacokinetic Property	Data
Systemic Bioavailability[+]	14-17%[+]
Peak Exposure[+]	12%[+]
Half-life (h)	BDP – 0.3 hours BMP – 4.5 hours
Protein Binding[+]	94-96%
Metabolism	CYP3A4 (>90% of BDP)
Excretion	~90% fecal, ~10% renal

[+]Calculated as percent of inhaled BDP

BDP = beclomethasone dipropionate; BMP = beclomethasone monopropionate; CYP3A4 = cytochrome; [+]As measured by plasma concentration of beclomethasone-17-monopropionate; BDP = Beclomethasone dipropionate; BMP = Beclomethasone-17-monopropionate; h = hours

Seasonal Allergic Rhinitis & Perennial Allergic Rhinitis

The efficacy of aerosolized BDP in patients with seasonal and perennial allergic rhinitis were separately assessed in one two week (SAR) and one six week (PAR) phase III, randomized, placebo-controlled, multicenter, parallel group study (**Table 2**).[10,11] Eligible participants were at least 12 years of age or older in good health with a documented history of SAR or PAR for the two week and six week trials, respectively. Exclusion criteria included history of nasal pathology and respiratory infection/disorder within the previous 14 days. In the SAR trial, after a 7-10 day run in period, a total of 338 patients were randomized to receive 320 mcg/day of BDP (N=167) or placebo (N=171).[10] In the PAR trial, after a 7-21 day placebo run in period, a total 474 patients from 35 centers were randomized to receive 320 mcg/day (two 80 mcg sprays in each nostril/day) of BDP (N=236) or placebo (N=238).[11]

In both trials, aerosolized BDP compared to placebo resulted in a statistically significant reduction in rTNSS scores (SAR[10]: Baseline- 9.6 BDP, 9.5 Placebo; LS Mean from Placebo: -0.91, p<0.001, 95% Confidence Interval [CI]: -1.3, -0.5; PAR[11]: Baseline- 8.9 BDP, 9.0 Placebo; LS Mean from Placebo: -0.84, p<0.001, 95% CI: -1.2, -0.5; **Table 3**). Treatment with BDP also led to statistically significant improvements in iTNSS scores (SAR[10]: Baseline- 9.0 BDP, 8.7 Placebo; least squares (LS) Mean from Placebo: -0.92, p<0.001, 95% CI: -1.3, -0.5; PAR[11]: Baseline- 8.1 BDP, 8.3 Placebo; LS Mean from Placebo: -0.78, p<0.001, 95% CI: -1.1, -0.4; **Table 3**).

Results from secondary outcomes also revealed significant results. In the two week SAR study, patients in the intervention group showed significant improvements from baseline in average ocular symptoms scores (LS mean treatment difference: -0.56 [95% CI: -0.9, -0.2]; P = 0.002).[10] Patients also achieved substantial improvements in individual ocular symptoms including improvements in itching/burning, tearing/

Table 2 | Summary of Beclomethasone Dipropionate Clinical Trials in Patients with Seasonal and Perennial Allergic Rhinitis

FDA Approval Studies

Study	Patients	Design	Outcomes	Interventions
Phase II Dose Ranging[6]	≥12yrs & Hx of SAR for ≥2 yrs with (+) skin test	N=245 DB R PC	**1°**: Avg of AM&PM Patient reported rTNSS over 2 wks **2°**: Avg of AM&PM Patient reported iTNSS over 2 wks; RQLQ at week 2; 24hr ocular/non-nasal symptom score	80mcg, 160mcg, 320mcg of BDP vs. placebo
Phase III SAR[10]	≥12yrs & Hx of SAR to pollen	N=338 DB R PC	**1°**: Avg of AM&PM Patient reported rTNSS over 2 wks **2°**: Avg of AM&PM Patient reported iTNSS over 2 wks; RQLQ at week 2; Avg AM&PM patient reported ocular symptom score	320mcg/day once daily vs. placebo
Phase III PAR[11]	≥12yrs & Hx of PAR	N=474 DB R PC	**1°**: Avg patient reported rTNSS over 6 wks **2°**: Avg patient reported iTNSS over 6 weeks; RQLQ at wk 6	320mcg/day once daily vs. placebo

Additional Studies

Study	Patients	Design	Outcomes	Interventions
Phase III Long Term Safety in PAR[12]	≥12yrs & Hx of PAR for ≥2 yrs; Sensitivity by skin test to at least one PAR allergen	N=526 DB R PC	**1°**: 24hr rTNSS AT 52 wks **2°**: TNSS over 30 weeks; RQLQ up to 52 wks	320mcg/day once daily vs. placebo
Phase III SAR ages 6-11[13]	6-11 yrs & Hx of SAR for ≥2 yrs	N=715 DB R PC	**1°**: Avg of AM&PM Patient reported rTNSS over 2 wks **2°**: Avg of AM&PM Patient reported iTNSS over 2 wks	80mcg/day, 160mcg/day for 15 days vs. placebo

Avg = Average; BDP = beclomethasone dipropionate; DB = Double Blind; Hx = History; iTNSS = instantaneous total nasal symptom scores; PAR = perennial allergic rhinitis; PC = Placebo Controlled; R = Randomized; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire; rTNSS = reflective total nasal symptom scores; SAR = seasonal allergic rhinitis; Yrs = Years; Wks = Weeks

watering, and redness of the eyes over the two week intervention period.[10]

In both the SAR and PAR studies, the intervention group, compared to placebo, had significant improvements in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (SAR[10]: -0.48 [95% CI: -0.8, 0.1]; p=0.005; PAR[11]: -0.58 [95% CI: -0.9, -0.2]; p=0.001). One notable limitation of these two studies was the short duration (2-6 weeks). Most patients with SAR and PAR have symptoms that outlast these short term trials making the long-term efficacy of BDP unclear.

Pediatric Seasonal Allergic Rhinitis

The efficacy of BDP was also evaluated in pediatric patients with a diagnosis of SAR.[13] Eligible participants were at least 6-11 years of age with a documented history of SAR for at least two years and demonstrated sensitivity to at least one seasonal allergen (verified by skin prick test). Exclusion criteria included nasal pathology, history of respiratory infection within previous 14 days, or active asthma requiring treatment with any drug.[13]

Patients were randomized to once daily treatment with BDP 80 mcg (N=239), BDP 160 mcg (N=242), or placebo (N=234). The primary endpoint was the average AM and PM subject-reported rTNSS over a two week period.[13]

Subjects in the intervention group experienced significantly greater AM and PM reductions in rTNSS from baseline compared to placebo (-0.71 [95%CI: -1.1, -0.3] for 80 mcg; -0.76 [95%CI: -1.1, -0.4] for 160 mcg; p<0.001 for both; **Table 3**). Patients also experienced significant changes from baseline in iTNSS compared to placebo (-0.63 [95%CI: -1.0, -0.3] for 80 mcg; -0.73 [95%CI: -1.1, -0.4] for 160 mcg; p<0.001 for both; **Table 3**) indicating that BDP provides effective relief of nasal symptoms.[13]

Adverse Events

In clinical trials ranging from 2 to 52 weeks in duration, nasal discomfort, epistaxis, and headache were the most commonly reported adverse effects compared with placebo (**Table 4**).[12]

Glaucoma and cataract formation were assessed using ocular tests involving intraocular pressure re-

Table 3 | Efficacy Summary of Beclomethasone Dipropionate in Clinical Trials [6,10,11,13]

		Treatment	N	Baseline (SD)	LS Mean (SE) Change from Baseline	Difference From Placebo		
						LS Mean	95% CI	p Value
Reflective Total Nasal Symptom Scores (rTNSS)	SAR	BDP 320 mcg/day	167	9.6 (1.51)	-2.0 (0.16)	-0.91	-1.3, -0.5	<0.001
		Placebo	171	9.5 (1.54)	-1.0 (0.15)			
	PAR	BDP 320 mcg/day	232	8.9 (1.70)	-2.5 (0.14)	-0.84	-1.2, -0.5	<0.001
		Placebo	234	9.0 (1.73)	-1.6 (0.14)			
Instantaneous Total Nasal Symptom Scores (iTNSS)	SAR	BDP 320 mcg/day	167	9.0 (1.74)	-1.7 (0.15)	-0.92	-1.3, -0.5	<0.001
		Placebo	171	8.7 (1.81)	-0.8 (0.15)			
	PAR	BDP 320 mcg/day	232	8.1 (1.98)	-2.1 (0.13)	-0.78	-1.1, -0.4	<0.001
		Placebo	234	8.3 (1.96)	-1.4 (0.13)			
Pediatric PAR		**Age 6–11 years**			**QNASL 160 mcg/day N = 242**		**QNASL 80 mcg/day N = 239**	
		rTNSS vs. Placebo (P-value)			-0.76 95% CI: -1.1, -0.4 (< 0.001)		-0.71 95% CI: -1.1, -0.3 (< 0.001)	
		rTNSS vs. Baseline (P-value)			-0.73 95% CI: -1.1, -0.4 (< 0.001)		-0.63 95% CI: -1.0, -0.3 (< 0.001)	

BDP = beclomethasone dipropionate; CI = confidence interval; iTNSS = Instantaneous Total Nasal Symptoms; LS = least squares; PAR = Perennial Allergic Rhinitis; rTNSS = Reflective Total Nasal Symptoms; SD = standard deviation; SE = standard error

cordings and slit lamp examinations in 245 patients treated with BDP nasal aerosol 320 mcg/day (N=197) or placebo (N=48). At the conclusion, only 10 patients (5%) in the intervention group and 1 (2%) in the placebo group had an intraocular pressure >21 mmHg.[10-14]

In a separate safety trial, BDP (320 mcg/day) was comparable to placebo with respect to 24 hour serum cortisol levels indicating that treatment with BDP nasal aerosol is not associated with hypothalamic-pituitary-adrenal-axis suppression in patients with PAR.[14,15]

Table 4 | Summary of Common Adverse Effects in Clinical Trials [6,10-15]

	QNASL Nasal Aerosol 320 mcg n (%)	Placebo n (%)
Nasal Discomfort	30 (5.2)	28 (4.8)
Epistaxis	11 (1.9)	7 (1.2)
Headache	13 (2.3)	9 (1.6)
IOP >21 mmHg	10 (5%)	1 (2%)

IOP = Intraocular Pressure; n = number

Dosing and Administration

Qnasl® is administered as an intranasal spray for the treatment of seasonal or perennial allergic rhinitis in patients 12 years or older. Qnasl® is formulated as a dry nasal aerosol. It must be primed with four actuations upon first use and 2 primes after 7 days of no use.[6]

Qnasl® is dosed at 320 mcg/day and is offered in one strength (80 mcg /spray) administered as 2 nasal sprays into each nostril once daily (4 sprays total for a daily dose of 320 mcg). The maximum daily dose is 4 nasal sprays per day.[6]

Cost

A one month supply of Qnasl® currently costs $138.99. In order to qualify for the loyalty card program, which offers Qnasl® at no more than $25/month, patients must meet the following criteria[17]:

- You are not a resident of Massachusetts.
- The person using the card is > 12 years of age.
- Your prescriptions are not paid for in part or in full by any state or federally funded programs, including but not limited to Medicare or Medicaid, Medigap, VA, DOD, TRICARE.
- Prescription is not reimbursed in full (including co-pay) by any third-party payer.

Summary

Qnasl® is the first in class dry intranasal steroid aerosol for the treatment of seasonal or perennial allergic rhinitis in patients 12 years of age or older. Qnasl® is effective in managing nasal symptoms associated with allergic rhinitis and has been evaluated in 1,049 patients. The Qnasl® recommended dosage is 320 mcg administered as two nasal aerosol sprays in each nostril once daily. Qnasl® is well tolerated with the majority of patients reporting nasal discomfort, epistaxis, and headache as the most common adverse events. Qnasl® offers patients an additional treatment option for seasonal or perennial allergic rhinitis, especially in patients who cannot tolerate aqueous or "wet" intranasal dosage forms that often cause post nasal medication drip and nasal discomfort.

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AVANAFIL (STENDRA®): THE NEWEST PHOSPHODIESTERASE 5 INHIBITOR

Erica Willcoxon, Pharm.D. Candidate

Erectile dysfunction (ED) effects an estimated 18 million men in the United States.[1] Possible etiologies include vascular, neurologic, hormonal and psychological factors. Most cases of ED result from vascular disturbances of the endothelium, similar to cardiovascular disease. Consequently, the prevalence of ED is highly correlated to the presence of one or more cardiovascular risk factors including hypertension, diabetes, and heart disease. Management of associated diseases is important when treating a patient with ED.[2]

The treatment of ED has progressed considerably over the past fifteen years. Before the late 1990s, ED was typically treated with surgery. As the physiological process of an erection was elucidated and used to develop pharmacological therapies, namely phosphodiesterase 5 (PDE5) inhibitors, treatment shifted to the primary care setting.[3]

The American Urological Association guidelines recommend PDE5 inhibitors as first line therapy for the treatment of ED.[2] In 2010, the three currently marketed PDE5 inhibitors, sildenafil, tadalafil, and vardenafil, amassed over two billion dollars in combined retail sales and over 17 million prescriptions dispensed.[4,5] Vivus developed the newest PDE5 inhibitor, avanafil (Stendra®) which was approved by the FDA for treatment of ED in April 2012. Avanafil is fast acting and highly selective for PDE5 which provides advantages over the currently available therapies on the market.[6] This article will discuss the pharmacology, clinical trials, efficacy, and tolerability of avanafil as well as examine the pharmacokinetic and pharmacodynamic properties that distinguish it from the other PDE5 inhibitors.

Pharmacology and Pharmacokinetics

Erection of the penis involves the release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation and inflow of blood to the corpus cavernosum. PDE5 is responsible for the degradation of cGMP in the corpus cavernosum. By inhibiting PDE5, avanafil causes increased levels of cGMP resulting in relaxation of the smooth muscle of the corpus cavernosum and an inflow of blood.

Avanafil is a selective inhibitor of cGMP-specific PDE5. An in vitro study comparing the inhibitory effects of avanafil with that of sildenafil, tadalafil, and vardenafil on the different PDE isoenzymes concluded that avanafil exhibits strong specificity and selectivity towards PDE5 compared to all other PDE isoenzymes (**Table 1**). Avanafil showed higher selectivity for PDE5 over PDE6 (>120-fold) than sildenafil (16-fold) and vardenafil (21-fold), and higher selectivity for PDE5 over PDE1 (>10,000-fold) compared with sildenafil (375-fold) and vardenafil (>1000-fold). Avanafil also had higher selectivity for PDE5 over PDE 11 (>19,000-fold) compared with sildenafil, vardenafil and tadalafil.[7]

Avanafil is rapidly absorbed with a median time to maximum concentration (T_{max}) of 30 to 45 minutes (Table 2). When taken with high fat meals, T_{max} is delayed by 1.12 to 1.25 hours, the maximum plasma concentration (C_{max}) is reduced by 24% (100 mg dose) and 39% (200 mg dose), and the area under the curve (AUC) is decreased 3.8%. These small changes in C_{max} and AUC are considered clinically insignificant; therefore, avanafil may be administered without regard to food. It is approximately 99% bound to plasma proteins. Avanafil is hepatically metabolized by cytochrome P-450 (CYP) 3A4 with minor contributions from CYP2C to two major metabolites, M4 and M16. M4 accounts for 4% of the pharmacologic activity of avanafil and M16 is inactive against PDE5.[8] Avanafil is excreted as metabolites predominately in the feces (approximately 62%) and to a lesser extent in the urine (approximately 21%). Avanafil has a terminal elimination half-life of 5 hours.

Table 1 | PDE Isoenzyme Selectivity versus PDE5 (fold difference) [7]

PDE isoenzyme	Avanafil	Sildenafil	Vardenafil	Tadalafil
PDE1	10,192	375	1,012	10,500
PDE3	>19,231	16,250	26,190	>25,000
PDE5 (reference)	1	1	1	1
PDE6	121	16	21	550
PDE9A	>19,231	2,250	16,667	>25,000
PDE11A	>19,231	4,875	5,952	25

PDE: phosphodiesterase

Clinical Trials

Three major randomized, double-blind, placebo-controlled trials have been completed with avanafil. Reduced response rates with other PDE5 inhibitors have been seen in patients with diabetes and in men who have undergone radical prostatectomy.[9] Therefore, two of the avanafil trials focused specifically on these subsets of patients to evaluate its efficacy and safety.

The REVIVE Trials

The REVIVE Trial was a randomized, double blind, placebo-controlled, phase 3 study of avanafil in 646 men with a history of ED for at least six months (**Table 3**).[10] The mean duration of ED was 6.5 years. Patients underwent a four week non-treatment run-in period followed by 12 weeks of treatment with one of the three strengths of avanafil (50, 100, or 200 mg) or placebo. Participants were instructed to attempt sexual intercourse 30 minutes after administering a dose of avanafil. The primary efficacy endpoints were improvement in the International Index of Erectile Function (IIEF)-erectile function (EF) domain score and the Sexual Encounter Profile (SEP) questions 2 and 3. The IIEF-EF domain is a 30 point questionnaire where a higher score represents better erectile function. The questionnaire was given at baseline then at 4 week intervals throughout treatment. The SEP questions were addressed after each time a patient made a sexual attempt throughout the trial. SEP question 2 (SEP2) asked "Were you able to insert your penis into your partner's vagina?" and SEP question 3 (SEP3) asked "Did your erection last long enough for you to have successful intercourse?" All three doses of avanafil demonstrated statistically significant improvement in the 3 primary outcomes as compared to placebo. A greater change from baseline in IIEF-EF domain scores, SEP2, and SEP3 were observed in a dose dependent manner with greater improvements seen in the avanafil 200 mg group as compared with the avanafil 50 mg and 100 mg groups. Secondary analysis demonstrated successful intercourse by couples within 15 minutes of taking avanafil. The most common side effects were headache, flushing, and nasal congestion

Table 3 | Results of the REVIVE Trials

		Change from Baseline	
Trial	**IIEF-EF Domain Score**	**SEP2(%)**	**SEP3(%)**
REVIVE [10]			
Avanafil 50 mg; N=154	5.4 (p=0.0014)	18.2% (p=0.0009)	27.8% (p=0.0002)
Avanafil 100 mg; N=157	8.3 (p<0.0001)	27.7% (p<0.0001)	43.4% (p<0.0001)
Avanafil 200 mg; N=156	9.5 (p<0.0001)	29.8% (p<0.0001)	44.2% (p<0.0001)
Placebo; N=155	2.9	7.1%	14.1%
REVIVE-D [12]			
Avanafil 100 mg; N=126	4.5 (p<0.0017)	21.5% (p<0.0004)	28.7% (p<0.0001)
Avanafil 200 mg; N=126	5.4 (p<0.0001)	25.9% (p<0.0001)	34% (p<0.0001)
Placebo; N=127	1.8	7.5%	13.6%
REVIVE-RP [14]			
Avanafil 100 mg; N=94	3.5 (p<0.001)	15% (p<0.001)	18% (p<0.001)
Avanafil 200 mg; N=96	5.2 (p<0.001)	21% (p<0.001)	21% (p<0.001)
Placebo; N=96	0.1	0%	5%
Open-Label Extension [15]			
Avanafil 100 mg; N=147	8.6	39.2%	54.4%
Avanafil 100 mg and 200 mg; N=535	10.8	36.4%	54.9%

IIEF-EF: International Index of Erectile Function-erectile function; SEP: Sexual Encounter Profile

and no drug related serious adverse events were reported.[10]

Erectile Dysfunction is present in over 70% of men with diabetes.[11] The REVIVE-D trial studied the efficacy and safety of avanafil in 390 ED patients with type 1 or type 2 diabetes (**Table 3**).[12] This randomized, double-blind, placebo-controlled study evaluated patient's response to avanafil 100 mg, avanafil 200 mg, or placebo for on-demand use for 12 weeks. Co-primary endpoints included changes in SEP2, SEP3, and IIEF-EF score. Statistically significant improvements in all primary endpoints were seen with both the 100 mg and 200 mg dose of avanafil compared to placebo ($p \leq 0.002$). A greater change from baseline in IIEF-EF domain scores, SEP2, and SEP3 were observed in a dose dependent manner with greater improvements seen in the avanafil 200 mg group as compared with the avanafil 100 mg group. Subgroup analyses demonstrated improvements in the percentage of successful intercourse attempts with both doses of avanafil and were observed regardless of diabetes classification (type 1 or 2), duration of diabetes history, or ED severity. Most participants attempted intercourse between 15 and 45 minutes after dosing but some subjects were able to achieve successful intercourse in 15 minutes or less after dosing. The most commonly reported adverse events were similar to those in the REVIVE trial which included headache, flushing, and sinus congestion. There were no drug-related serious adverse events and no deaths reported during the study.[12]

More than half of men with bilateral, nerve-sparing radical prostatectomy experience ED 18 months after surgery.[13] The REVIVE-RP trial evaluated the safety and efficacy of avanafil in men following bilateral, nerve-sparing radical prostatectomy (**Table 3**).[14] This randomized, double-blind, placebo-controlled study included 298 ED patients who received avanafil 100 mg, 200 mg or placebo for 12 weeks. Primary endpoints were changes from baseline in SEP2, SEP3, and IIEF-EF score. Treatment with both doses of avanafil was associated with significant improvements compared to placebo in all 3 co-primary endpoints ($p<0.001$). A greater change from baseline in IIEF-EF domain scores, SEP2, and SEP3 were observed in a dose dependent manner with greater improvements seen in the avanafil 200 mg group as compared with the avanafil 100 mg group. Successful intercourse attempts were made within 15 minutes of dosing in 50% of the avanafil 100 mg treatment group and 33% of the avanafil 200 mg treatment group. The most common adverse reactions were mild and included headache, flushing, and nasal congestion. No serious adverse events and no deaths occurred during this study.[14]

A total of 712 patients who successfully completed the REVIVE or REVIVE-D trial were enrolled in an open-label, long-term extension study to evaluate the safety and tolerability of avanafil (**Table 3**).[15] All patients were initially started on avanafil 100 mg and at any point during the trial subjects could request to have their dose increased to 200 mg for improved efficacy or decreased to 50 mg for improved tolerability based on individual response to the drug. Primary endpoints were changes from baseline in SEP2, SEP3, and IIEF-EF domain score. The majority of participants (72%) escalated their dose to 200 mg. Of the 512 patients who increased their dose, 34% (N=172) were considered non-responders on the 100 mg dose. Sixty five percent (N=112) of avanafil 100 mg non-responders subsequently responded to treatment with the 200 mg dose. In subjects attempting sexual intercourse within 15 minutes of dosing, 80% of attempts were successful. The most frequent adverse effects were headache, nasopharyngitis, and flushing. There were no drug-related serious adverse events, no deaths, and no reports of hearing loss or priapism.[15]

Future Clinical Trials

FDA is requiring Vivus to conduct two post-marketing studies to address concerns about potential adverse events. The first clinical trial, to be completed by February 2013, will examine avanafil's effects on vision including visual acuity, intraocular pressure, pupillometry, and color vision discrimination. The second study will evaluate the effects of the drug on spermatogenesis and must be completed by November 2013.[16]

Dose and Administration

The recommended starting dose is 100 mg. Avanafil should be taken orally approximately 30 minutes before sexual activity. Based on a patient's tolerability and efficacy, the dose can be increased to a maximum of 200 mg or decreased to 50 mg. The lowest dose that provides benefit should be used. The maximum dosing frequency is once every 24 hours. Avanafil may be given without regards to meals.[8]

Patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) or mild to moderate renal insufficiency (creatinine clearance greater than or equal to 30 mL/min to less than 90 mL/min) dose adjustments are not necessary. Avanafil has not been studied in patients with severe hepatic disease or renal impairment; therefore, use in these patients is not recommended.[8]

Table 4 | Adverse Events with Avanafil versus Placebo [10,12,14]

Adverse Event	Avanafil 50 mg (N=217)	Avanafil 100 mg (N=349)	Avanafil 200 mg (N=352)	Placebo (N=349)
Headache	5.1%	6.9%	10.5%	1.7%
Flushing	3.2%	4.3%	4%	0%
Nasal congestion	1.8%	2.9%	2%	1.1%
Naso-pharyngitis	0.9%	2.6%	3.4%	2.9%
Back pain	3.2%	2%	1.1%	1.1%

Of the total number of subjects who participated in clinical trials of avanafil, approximately 23% were at least 65 years old. No overall differences in efficacy and safety were observed between patients over 65 compared to younger subjects; therefore no dose adjustment is warranted based on age.[8]

Adverse Events and Drug Interactions

Avanafil is generally well tolerated. Most adverse events were mild to moderate in severity with the most commonly reported events being headache and flushing (**Table 4**). In the open-label extension study, the discontinuation rate due to adverse reactions was 2.8%.[15]

Rare cases of prolonged erection, visual changes, and hearing loss have been reported in patients taking PDE5 inhibitors (< 1%). In the event an erection lasts longer than four hours, a patient should seek medical attention due to the possibility of penile tissue damage and permanent impotency. PDE5 inhibitors have demonstrated transient impairment of color discrimination, consistent with inhibition of PDE6 which is involved in phototransduction in the retina. While this side effect is unlikely due to avanafil's high selectivity for PDE5, in clinical trials one patient reported a change in color vision.[17] Use of PDE5 inhibitors have also been associated with a decrease or loss of hearing, accompanied by tinnitus or dizziness. A patient experiencing these symptoms should report it to their physician and discontinue use of avanafil.

Avanafil is contraindicated in patients taking nitrates due to enhanced hypotensive effects of this combination. In patients who have taken avanafil, and administration of a nitrate is deemed necessary in a life-threatening situation, at least 12 hours should elapse after the last dose of avanafil before administering the nitrate.[8]

Due to concerns of increased plasma concentrations, avanafil is not recommended for use in patients on concomitant strong CYP3A4 inhibitors. A maximum dose of 50 mg per day is recommended for patients on moderate CYP3A4 inhibitors (**Table 5**). Caution is advised when avanafil is administered to patients on alpha-blockers and other anti-hypertensive medications. Patients should be stable on their anti-hypertensive therapy before initiating avanafil. Initiate avanafil at 50 mg due to increased risk of symptomatic hypotension.[8]

Cost

Avanafil is set to be released to the US market by the end of 2012. It will be available in 50, 100, and 200 mg tablets in bottles of 30 or 100.[16] The average retail cost per five doses of the currently available PDE5 inhibitors are $119 for Viagra®, $129 for Cialis®, $118 for Levitra®, and $86 for Staxyn®.[18] Avanafil will likely be sold in this general price range.

Summary

The currently available PDE5 inhibitors have similarly high rates of successful sexual intercourse and similar side effect profiles.[19] Therefore, choosing a PDE5 inhibitor should be based on patient preferences, including ease of use, adverse effects, and cost. Avanafil is the newest option providers have when treating patients with erectile dysfunction. Side effects are typically mild and include headache, flushing, and nasal congestion. The recommended starting dose is 100 mg approximately 30 minutes before sexual activity. The dose can be increased to 200 mg or decreased to 50 mg based on individual response. It

Table 5 | Strong and Moderate CYP3A4 Inhibitors [8]

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Atazanavir	Amprenavir
Clarithromycin	Aprepitant
Indinavir	Diltiazem
Itraconazole	Erythromycin
Ketoconazole	Fluconazole
Nefazodone	Fosamprenavir
Nelfinavir	Verapamil
Ritonavir	
Saquinavir	
Telithromycin	

CYP: cytochrome P-450

has a faster onset of action which may provide benefit over other PDE5 inhibitors.

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Clinical Trial Update

Efficacy of the pertussis vaccine — According to the Centers for Disease and Prevention (CDC) over 27,000 cases of pertussis were reported in the US in 2010[1]; California in particular experienced a large outbreak with the number of incident cases reported being the highest since 1958.[2] Whole-cell pertussis vaccines have been replaced by the safer acellular pertussis vaccine which has been shown to lower the rate and also lessen the severity of pertussis infection. Acellular pertussis is a component of both the diphtheria-tetanus-acellular pertussis (DTaP) vaccine and the Tdap vaccine. Tdap is used more commonly in older children and adults and contains a reduced amount of pertussis antigen compared to the DTaP vaccine. Current CDC vaccination schedules recommend children receive 5 total doses of DTap between the ages of 2 months and 4-6 years. Adolescents aged 11-18 should receive a single dose of Tdap, preferably at age 11 or 12; adults aged 19-64 should also receive a single dose of Tdap.[1]

Recent outbreaks of pertussis have questioned whether the fifth and final childhood DTaP dose provide sufficient long-lasting protection to prevent disease. Klein and colleagues utilized data from a large health care system in California (Kaiser Permanente) to assess the potential waning protection offered by the DTaP vaccine between January 2006 and June 2011.[2] Subjects were included if they were positive or negative for pertussis (based on PCR testing) and received a DTaP vaccine between the ages of 47-84 months, which was considered as the fifth and final childhood DTaP dose. Subjects born before 1999 were excluded as this reflected the time when the whole-cell pertussis vaccine was completely replaced by the acellular version; additional exclusion criteria included receipt of Tdap after the fifth dose of DTap prior to PCR and cases where PCR was performed within two weeks of the fifth DTaP dose. Notably, the study period included the 2010 outbreak.

Case subjects were those who tested positive for pertussis who met inclusion criteria. The study included two control groups: the first group consisted of subjects who had a negative PCR test and the second group consisted of controls matched to each PCR positive case that did not undergo PCR testing. Controls were matched based on age, sex, race or ethnic group, and geographic location to the case subjects. The final study population included subjects aged 4 to 12 years, of which 99% received the recommended 5 doses of TdaP.[2]

The study included 277 children with a positive PCR, 3318 PCR-negative controls, and 6086 matched controls. Importantly, the investigators found that the risk of pertussis increased by 42% for each year after the last DTaP dose was administered when compared to either the group with a negative PCR test and the matched controls. Assuming the final DTap dose was 95% effective, this degree of waning efficacy would decrease the effectiveness to 71% after five years. Accordingly, a higher percent of PCR -positive cases were noted in older subjects: 18.5% in children 10 years of age compared to 4.5% in children 6 years of age. Length of time since the last DTaP dose was also positively associated with an increased chance of a positive PCR result; cases received their last DTaP dose significantly earlier than controls. Overall cases of pertussis were mild to moderate in severity as only 4% of cases had emergency department visits and there were no hospitalizations or deaths attributed to pertussis.[2]

Potential limitations include a lack of a control

population who did not receive the pertussis vaccination and retrospective nature of the study; therefore, conclusions can only be considered hypothesis generating and not causal.[2]

The apparent waning efficacy of the DTaP vaccine raises many questions regarding the optimal timing of future vaccinations once the childhood DTaP series is complete. As exact causes for the pertussis outbreak are unknown it is not clear what specific factors reduce the vaccine's efficacy and what measures, if any, can be undertaken to maintain the vaccine's efficacy and reduce the incidence of future outbreaks. The authors suggest the adolescent Tdap dose be given as early as possible, preferably at age 11 or 12 (coinciding with the CDC recommendations[1]), as a longer duration since previous DTaP vaccination was associated with an increased risk of incident pertussis.[2] Potential options to minimize the potential waning efficacy include administering the Tdap vaccination earlier than age 11 or 12 or replacing Tdap with the more antigenic DTaP , but these interventions require further study before they can be routinely recommended. Despite the apparent waning efficacy the vaccine appears to prevent significant morbidity and mortality as evidenced by the low number of hospitalizations and zero cases of death, and therefore the CDC recommended vaccine schedule[1] should be followed as recommended until further information is available.

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Thank You!

Happy 27th Anniversary! We are amazed to be in our 28th year of publication and it would not be possible without your support as a reader! We look forward to continuing to grow the PharmaNote and produce high-quality articles covering a variety of important and timely topics—hopefully the next 27 years will be as successful and rewarding as the first 27!

-Drs. Gums, Curry, and Dietrich—Editors

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