Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Phosphodiesterase 5 Inhibitors for the Treatment of Erectile Dysfunction***

-August 2018-

Background:

This Formulary Brief addresses the use of phosphodiesterase 5 inhibitors (PDE5i) for the treatment of erectile dysfunction (ED). In August 2014, the IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed PDE5i and their role in the treatment of ED. At that time ED was recognized as a prevalent disease and PDE5i efficacy was reviewed, however, no PDE5i were added to the formulary. Recently sildenafil citrate, the most commonly used PDE5i, has become available as generic on the open market resulting in a marked decrease in pricing, thus this drug class was reviewed at the August 2018 NPTC meeting to re-evaluate eligibility for addition to the IHS National Core Formulary (NCF). As a result of this pharmacotherapeutic review, **the NPTC voted to ADD "any PDE5i" to the NCF.**

Discussion:

Erectile dysfunction (ED) is defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance[2]. It is considered the most common sexual problem in men, affecting 30 million in the U.S. and 150 million worldwide[1]. The disease encompasses a spectrum of clinical situations: physical illness (organic), reaction to life stress (intrapsychic), and unhappy relationships (relational)[3].

Treatment is multi-faceted, including sexual education, individual and couple counselling, surgical/ procedural intervention, and pharmacologic therapy[2]. Independent risk factors for ED include age (ED affects 37% of men 70-75 years old), smoking, diabetes mellitus (20% of men with ED), hypertension (38-42% of men with ED), dyslipidemia (42% of men with ED), depression (11% of men with ED), and obesity/metabolic syndrome[2]. Both ED and cardiovascular disease (CVD) are thought to have origins in endothelial dysfunction, thus ED is thought to be a harbinger of CVD in men with risk factors[3]. While there is no data on the incidence and prevalence of ED in American Indians and Alaska Natives (AI/AN), the prevalence of CVD may act as a surrogate. CVD is the leading cause of death in AI/AN with the CVD death rate 20% greater among AI/AN (1996–1998) than among all U.S. races (1997)[4]. AI/AN die from heart diseases at younger ages than other racial and ethnic groups in the U.S., with 36% of those dying before 65 years of age[4]. Thus, diagnosis and treatment of ED in the AI/AN population may raise awareness of CVD and improve other quality of life markers.

PDE5i are first line therapy for the treatment of ED according to urologic societies worldwide. The mechanism of action is inhibition of the phosphodiesterase 5 enzyme, which breaks down cGMP in the corpus cavernosum. This allows increased smooth muscle relaxation and blood inflow in the setting of sexual stimulation resulting in penile engorgement[1]. Four PDE5i are currently FDA approved for the treatment of ED: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®), and avanafil (Stendra®). Only tadalafil is indicated for daily dosing, all others are dosed as needed prior to sexual activity. Pharmacodynamically, these medications differ in their time to onset and duration of activity[5,6,7,8].

Drug	Time to Onset	Duration of Activity	Onset Delayed by High Fat Meal
Avanafil	15 minutes	6 hours	Yes
Vardenafil	20-30 minutes	8-12 hours	Yes
Sildenafil	30-60 minutes	2-4 hours	Yes
Tadalafil	60-120 minutes	36 hours	No

Administration of the medications with a high fat meal (with the exception of tadalafil) will delay the onset of action by at least one hour. Common adverse drug reactions across the class include flushing, headache, rhinitis, dizziness, myalgia, and back pain[5,6,7,8]. Vision loss, hearing loss and priapism are important serious adverse effects which patients should be informed of prior to starting these medications. PDE5i are contraindicated for use in patients with unstable angina, severe congestive heart failure (CHF), uncontrolled hypertension, high-risk arrhythmias, and those receiving nitrates[15]. Use of PDE5i in patients on alpha-blockers should be done with close monitoring for hypotension[3]. All PDE5i are metabolized by the CYP3A4 enzyme and interact with CYP3A4 inhibitors and potentiaters[5,6,7,8.]

Efficacy of PDE5i in the treatment of ED is excellent when assessed in placebo-controlled trials of all FDA approved medications in this class[9,11]. In head-to-head trials and meta-analyses, adverse events were similar between tadalafil and sildenafil with a slightly lower incidence of flushing and higher incidence of myalgia with tadalafil[10]. In a trade-off network meta-analysis, Chen et al. concluded that sildenafil 50mg appeared to have highest efficacy while tadalafil 10mg was the most tolerable[11]. Response to dose increases in all PDE5i are small and non-linear[2]. Daily dosing of PDE5i (tadalafil and vardenafil only) does not significantly improve post-treatment satisfaction scores compared to the same medication dosed on demand[2]. The Cochrane Database Reviews of PDE5i confirm efficacy and a favorable safety profile for these medications in the treatment of ED[12]. Analysis of 10 years of adverse event (AE) data showed 16.2% of AEs were cardiovascular in nature and 5% were deaths[16] although a review of all published clinical trials as of 2013 did not find a statistically significant difference in myocardial infarction (MI) or cardiovascular-related deaths between placebo and active PDE5i drug[15]. In 2016, analysis of 43,000 patients from the Swedish Patient Register found that the incidence rate of MI was higher in men with ED not treated with PDE5i, along with a 33% reduction in all-cause mortality and a 40% reduction hospitalization for heart failure[17], thus supporting safe use of PDE5i in patients with heart failure and left ventricular hypertrophy. Four studies analyzed the association between PDE5i and risk of melanoma with a small, although not causal, association of PDE5i therapy and incidence of low grade melanoma[18,19].

Findings:

ED is a common disease affecting a large proportion of the male population. While no data exists specifically for AI/AN, the incidence of independent risk factors as well as CVD make it likely to effect a large portion of the AI/AN population. PDE5i are first line treatment for ED. They are considered safe and effective. While efficacy is highest with sildenafil, tadalafil has a more favorable side effect profile. Adherence to all PDE5i therapy was excellent, but tadalafil (as needed) had the highest adherence rate. In review of utilization data for the IHS, sildenafil is most commonly prescribed. Considering the low cost of sildenafil, this will likely be the PDE5i added to most formularies, however given adherence and efficacy data of long acting PDE5i along with several expiring patents, “any PDE5i” was added to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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