Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Neuraminidase Inhibitors***
-February 2016-

Background:
Influenza and pneumonia constitute the leading cause of death from infectious disease in the United States. The age-adjusted death rate from these conditions among American Indians and Alaska Natives (AI/AN) is 1.5 times higher than in the general population. The prevention and effective treatment of influenza is a top priority in the Indian Health Service (IHS) requiring a multi-modal approach to reduce disease burden in Indian country. While influenza vaccination remains the single most effective strategy for the prevention of influenza and its complications, anti-viral therapy has been advocated as an adjunct by public health organizations including the World Health Organization and the U.S. Centers for Disease Control and Prevention (CDC).

Discussion:
There are two general classes of anti-viral medications for both the prophylaxis and treatment of influenza, adamantanes and neuraminidase inhibitors. Due to widespread resistance among contemporary influenza strains, adamantanes such as amantadine and rimantidine are no longer recommended for use.

Neuraminidase inhibitors, including oseltamivir, zanamivir, and peramivir are advocated as the sole class of anti-viral medications for the prevention and treatment of influenza. The mechanism of action of neuraminidase inhibitors is the competitive inhibition of neuraminidase on the surface of both Influenza A and Influenza B viruses.

According to its guidance issued for the 2015-2016 influenza season, the CDC recommends all three neuraminidase inhibitors for both the prevention and treatment of influenza. Oral oseltamivir is the preferred agent for pregnant women and hospitalized patients, although intravenous peramivir is an alternative for those who cannot tolerate enteric medication. Because zanamivir is administered as an aerosol, caution is advised regarding potential adverse respiratory effects and should generally be avoided among persons with pre-existing chronic lung disease.

The CDC recommends treatment for any patient with confirmed or suspected influenza who is hospitalized, has severe or progressive illness, or at high-risk for complications including AI/AN adults and children. Treatment decisions should not await laboratory confirmation.

While the CDC does not generally recommend pre-exposure prophylaxis, for post-exposure prophylaxis, anti-viral medications are recommended as an adjunct (not a replacement) to vaccination. Provided that medication can be started within 48 hours of exposure, for those at high risk of influenza complications, chemoprophylaxis is recommended for people who cannot be immunized, are within two weeks of vaccination, or are unlikely to respond to vaccination due to severe immunodeficiency.

Despite longstanding recommendations from public health organizations, the use of neuraminidase inhibitors has been considered controversial by some experts. The principal controversy pertains to concerns about the efficacy of the medications in reducing influenza-related morbidity and mortality. Following accusations of publication bias related to claims made in industry-supported drug trials, in 2014 the Cochrane Collaboration published a systematic review of all randomized control trial (RCT) data.

In summarizing the findings of their review, the Cochrane authors noted that both oseltamivir and zanamivir reduced the time to symptomatic improvement of influenza-like illness but only by about half a day, which may not be superior to the use of anti-pyretic agents. They found no credible evidence for reduction in the risk of complications of influenza, including pneumonia, hospitalization or death. Specifically, no evidence was found for these benefits in children or adults considered at high risk. They also found little evidence to support use of these agents for chemoprophylaxis.

In response to the Cochrane analysis, both the CDC and the Infectious Disease Society of America (IDSA) re-iterated their recommendations regarding the use of neuraminidase inhibitors for the treatment of influenza. The rationale for this recommendation was two-fold. First, the ISDA noted that the RCT data in the Cochrane analysis involved treatment of healthy outpatients with mild illness and included both patients proven to be influenza infected as well as those with influenza-like illness. This was felt to underestimate the treatment efficacy of neuraminidase inhibitors.

Second, the CDC and IDSA cited consistent observational studies among hospitalized patients with both seasonal and pandemic flu during 2009 that documented reductions in serious outcomes including ICU admission and death. They also noted that while no RCT was powered to evaluate the effect of oseltamivir treatment of outpatients to reduce influenza-associated complications such as hospitalization or lower respiratory tract infections, pooled RCT data demonstrated a reduction in clinician-diagnosed lower respiratory tract infections requiring antibiotics.

Findings:
Influenza is a major source of morbidity and mortality in the United States and AI/AN patients are at higher risk both from infection and influenza-related complications.

There is widespread agreement that influenza vaccination remains the single most effective strategy in reducing the risk both of influenza infection and its complications.

Randomized control trial data show a modest benefit from use of neuraminidase inhibitors among healthy outpatients, primarily in reducing the time to alleviation of symptoms. RCT data was not adequately powered to assess benefit in reducing risk of influenza-related complications or death. Multiple observational studies have cited the potential benefits of neuraminidase inhibitors in reducing morbidity and mortality from influenza during the 2009 H1N1 influenza pandemic. Neuraminidase inhibitors continue to be recommended by public health experts for both treatment and prevention of influenza among high-risk groups, including AI/AN children and adults.

Based on limited clinical advantages of neuraminidase inhibitors noted in current reviews of influenza treatment and prophylaxis, the NPTC did not add a neuraminidase inhibitor to the National Core Formulary.

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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