Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Treatment of Influenza***

-November 2019-

Background:

In November 2019, the National Pharmacy and Therapeutics Committee (NPTC) reviewed the clinical guidelines and current, approved pharmacotherapeutic options for the treatment and prevention of seasonal influenza. The NPTC previously reviewed this topic in 2016, however no formulary agents for influenza treatment and/or prophylaxis were added at that time. Following the 2019 NPTC clinical and pharmacoeconomic analyses, the NPTC voted to **add oseltamivir to the National Core Formulary.**

Discussion:

Influenza is a contagious respiratory illness caused by influenza viruses. Signs and symptoms of influenza include fever, cough, sore throat, runny or stuffy nose, muscle or body aches, headache, fatigue, vomiting or diarrhea. Diagnosis can be confirmed by rapid influenza diagnostic tests or rapid molecular assays, although treatment decisions should be based on clinical diagnosis, especially in high-risk patients. According to the CDC, 49 million cases of influenza were reported during the 2017–2018 influenza season, with an estimated 960,000 hospitalizations and 79,000 influenza-related deaths[1]. High risk groups include individuals with asthma or COPD, heart disease, renal or hepatic impairment, as well as American Indians and Alaska Natives (AI/AN)[2]. Pneumonia is a known complication of influenza[3]. In 2017, the CDC reported that influenza and pneumonia were among the top ten causes of death in the US. Influenza and pneumonia were the ninth leading cause of death in the AI/AN population in 2017[4].

The annual influenza vaccine is far and away the single most effective means of primary prevention for seasonal influenza and should be offered to all patients each year, according to CDC guidelines. For those individuals diagnosed with or exposed to influenza, multiple antiviral therapy options exist. Currently, there are three FDA-approved neuraminidase inhibitor agents and one endonuclease inhibitor agent for the treatment of influenza. These agents include oseltamivir, zanamivir, peramivir, and baloxavir marboxil respectively. Of these, oseltamivir, zanamivir, and baloxavir marboxil are also approved for chemoprophylaxis of influenza[5]. Comparatively, baloxavir marboxil, which received FDA approval in October 2018, offers the advantage of requiring a single oral dose for the treatment of uncomplicated influenza. According to the Infectious Disease Society of America guidelines, adamantane-based antiviral agents are not recommended for the treatment or chemoprophylaxis of influenza due to widespread resistance[6].

A 2017 meta-analysis of 9 international, community and outpatient centers (N=3376) reviewed the rate of H1N1 influenza A-related hospital admissions in patients given neuraminidase inhibitors. Results showed that in those patients with confirmed or suspected influenza, neuraminidase inhibitors significantly reduced the likelihood of requiring hospital admission in children (OR: 0.25; 95% CI: 0.18-0.34) and adults (OR: 0.26; 95% CI: 0.19-0.35), compared to no treatment[7]. A second 2017 meta-analysis reviewed the impact of neuraminidase inhibitors on influenza in 20,634 international patients, of which 29% had radiologically-confirmed influenza-related pneumonia. The authors concluded that in patients with influenza-related pneumonia who received neuraminidase inhibitors, early treatment (within 2 days of symptom onset) versus later treatment significantly reduced both mortality (OR=0.7; 0.55-0.88, p=0.003) and the need for ventilator support (OR=0.68; 0.54-0.85, p=0.001)[8].

A 2017 observational cohort study and meta-analysis evaluated the safety of neuraminidase inhibitors during pregnancy and the risk of adverse neonatal outcomes and congenital malformations. Only oseltamivir and zanamivir were included in the review[9]. Pre-specified study outcomes included low birth weight, low Apgar score, preterm birth, small-for-gestational-age birth, stillbirth, neonatal mortality, neonatal morbidity, and congenital malformations. Results showed that exposure to neuraminidase inhibitors in utero was not associated with low birth weight (OR=0.77; 0.65-0.91), small-for-gestational-age birth (OR=0.72; 0.59-0.87), or neonatal morbidity (OR=0.92; 0.86-1.0). Importantly, none of the aforementioned study outcomes were significantly increased when results were restricted to patients who received oseltamivir.

The following overall conclusions were drawn from the literature search pertaining to the neuraminidase inhibitors. Neuraminidase inhibitors significantly decrease the likelihood of influenza-related hospital admission in children and adults. Early treatment with neuraminidase inhibitors can reduce mortality. Neuraminidase inhibitors display efficacy in influenza prophylaxis. Neuraminidase inhibitors are not associated with low birth weight or neonatal morbidity when exposed in utero[7-9].

=Guidelines=

The Infectious Disease Society of America (IDSA) guidelines recommend that clinicians initiate antiviral treatment as soon as possible in patients with documented or suspected influenza who meet specified criteria. Use of a single neuraminidase inhibitor (either oral oseltamivir, inhaled zanamivir, or intravenous peramivir) is strongly recommended *(Level A-1)* while combination use of neuraminidase inhibitors is discouraged. Clinicians should treat uncomplicated influenza in otherwise healthy ambulatory patients for 5 days with oral oseltamivir or inhaled zanamivir, or a single dose of intravenous peramivir *(A-1).* Per the IDSA, baloxavir marboxil is an endonuclease inhibitor approved by the FDA for treatment of acute uncomplicated influenza in patients aged ≥12 years who have been symptomatic for no more than 48 hours. As FDA approval occurred after finalization of these guidelines, the panel was unable to make recommendations on use of baloxavir[6].

The 2019 American Academy of Pediatrics (AAP) influenza guidelines recognize oseltamivir as their antiviral drug of choice but state that zanamivir is an equally acceptable alternative[10]. When indicated, the AAP encourages timely administration of antiviral medications and recommends use in high-risk children with either suspected or confirmed influenza for the treatment and/or prophylaxis of influenza illness. The efficacy of antiviral medications reported in studies is greatest in patients with laboratory-confirmed influenza although the AAP recommends not delaying treatment while awaiting definitive influenza confirmation as early therapy provides the best outcomes.

Findings:

Annual influenza immunization remains the single most effective method for preventing influenza-related morbidity and mortality in AI/AN patients. Neuraminidase inhibitors offer clinicians a guideline-supported pharmacotherapeutic option in the treatment and chemoprophylaxis of seasonal influenza. Attention should be given to ensure clinicians prescribe neuraminidase inhibitors in accordance with guideline recommendations and evidence-based outcomes. Findings from published literature, clinical practice guidelines, and internal pharmacoeconomic and utilization analyses offered a value-based decisional opportunity which supported the addition of the neuraminidase inhibitor, oseltamivir, to the IHS 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.

References:

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