Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Hepatitis C Virus Treatment***
-November 2018-

Background:
The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed the pharmacological treatment of Hepatitis C Virus (HCV) infection at its Fall 2018 meeting. This topic was also reviewed by the NPTC in July 2012 and February 2015 though no medications were added to the National Core Formulary at that time. Following extensive clinical review, pharmacoeconomic evaluation and internal deliberation, the NPTC voted to **ADD (1.) glecaprevir/pibrentasvir (*Mavyret*®)**, **(2.) ledipasvir/sofosbuvir (*Harvoni*®),** and **(3.) sofosbuvir/velpatasvir (*Epclusa*®)** to the IHS National Core Formulary.

Discussion:
Hepatitis C virus infection is highly prevalent among American Indians and Alaskan Natives (AI/AN). The Centers for Disease Control and Prevention (CDC) estimate that 3.5 million American adults suffer chronic infection with HCV, though AI/ANs have the highest incidence of acute HCV infection and highest mortality rate from HCV-related deaths among any race/ethnicity[1-4]. In newly infected patients, 20-30% will develop symptoms of acute disease and 75-85% will progress to chronic HCV infection. In those with chronically infection, 60-70% will develop chronic liver disease, 5-20% will develop cirrhosis over a period of 20-30 years and 1-5% will die from either cirrhosis or liver cancer[5]. The highest risk population cohorts for HCV infection include (1) current or former injection drug users, (2) recipients of blood transfusions (before 1992) or clotting factors (before 1987), (3) hemodialysis patients, (4) HIV-infected persons, (5) infants born to HCV-infected mothers, and (6) persons with known exposure to HCV (e.g., healthcare workers with accidental needle-sticks)[5]. Epidemiologic data provides that approximately 50% of infected persons remain unaware of their HCV status[6]. Improved HCV screening, especially among those born between 1945 and 1965, is an important factor in identification and treatment of chronic HCV infection.

Several oral, direct-acting antiviral (DAA) medications are now available which are highly efficacious across the spectrum of HCV genotypes (1a, 1b, 2, 3, 4, 5, and 6). Of note, genotype 1a represents 60-70% of all HCV patients in the U.S. who are chronically infected[7,8]. While no estimates exist for the IHS patient population, anecdotal evidence from IHS subject matter experts suggests a similar genotypic pattern in AI/ANs as the general U.S. population. Multiple clinical trials demonstrate >90% sustained virologic response rates (SVR) at 12 weeks after treatment completion for most DAAs, without the use of ribavirin or interferon. Studies strongly associate successful SVR with reduced HCV-related morbidity and mortality[9,10]. Moreover, support from contemporary HCV guidelines[11] combined with improved DAA safety profiles, pan-genotypic effectiveness, patient tolerance and convenience, and the simplicity of the prescribing regimen support the value of DAAs in HCV treatment. Cost remains the most significant barrier to broad utilization.

Along with the aforementioned clinical considerations, the NPTC reviewed agency-specific DAA procurement and utilization trends as well as IHS pharmacoepidemiologic and pharmacoeconomic data in guiding a formulary decision. The following three DAAs were added to the National Core Formulary, offering prescribers a host of therapeutic options that address the majority of HCV patient treatment scenarios. Though no directly-comparative DAA studies are available, drug-specific characteristics and clinical outcomes are known and detailed below for prescriber consideration. All DAAs have labeling on the risk of Hepatitis B virus (HBV) reactivation in patients receiving DAAs who are co-infected with HCV and HBV. Testing for current or prior HBV infection (before initiating DAAs) and during HCV treatment is strongly recommended.

Glecaprevir/pibrentasvir (Mavyret®)
The glecaprevir/pibrentasvir combination consists of a nonstructural (NS) protein 3/4A protease inhibitor (glecaprevir 100mg) and a NS5A inhibitor (pibrentasvir 40mg), which treat HCV infection by inhibiting hepatitis C viral replication and/or virion assembly. Glecaprevir/pibrentasvir is approved for adults with all HCV genotypes without cirrhosis (treatment duration: 8 weeks) or with compensated cirrhosis (treatment

duration: 12 weeks). Use in treatment-experienced patients is limited by genotype and previous treatment regimens; duration varies with individual patient factors. With glecaprevir/pibrentasvir, three tablets must be taken daily with food. Contraindications include severe hepatic impairment and drug-drug interactions that include, but are not limited to, atazanavir or rifampin. Concomitant use with drugs that induce P-gp or CYP3A4 should be avoided. No dosage adjustments are necessary in patients with renal impairment, including those on dialysis. Results from numerous trials support glecaprevir/pibrentasvir in pan-genotypic HCV treatment of patients without cirrhosis, with compensated cirrhosis, with CKD (stage 4 and 5), with treatment-experienced patients, and those with HCV/HIV coinfection[6,12]. Glecaprevir/pibrentasvir is not an option, however, for decompensated cirrhosis due to the inclusion of a protease inhibitor. Nevertheless, the 8-week treatment course of glecaprevir/pibrentasvir for treatment-naïve, non-cirrhotic patients with HCV genotypes 1-6 make it potentially appealing from an adherence, safety and cost perspective.

Sofosbuvir/velpatasvir (Epclusa®)

The oral, fixed-dose combination of a NS5B polymerase inhibitor (sofosbuvir 400mg) and a NS5A inhibitor (velpatasvir 100mg) provides an alternative pan-genotypic HCV treatment option, albeit for 12-week durations in most patients. Sofosbuvir-velpatasvir requires only one tablet be taken daily with or without food, although an acidic environment is needed for optimal absorption. This may necessitate avoidance, substitution or delayed administration of acid-reducing medications (e.g., PPIs, H_2RAs). Concomitant use of amiodarone is also not recommended due to potential bradycardia. Other major drug interactions include avoiding P-gp inducers and/or moderate to potent CYP inducers including rifampin, St. John's wort, or carbamazepine. No contraindications are reported and standard dosing is safe with all stages of hepatic impairment. Safe doses of sofosbuvir in renally-impaired patients (eGFR<30ml/min) have not been established and are not recommended by HCV guidelines for use in CKD Stage 4 (<30 ml/min) or Stage 5 (end-stage renal disease)[11]. Clinical trials support the use of sofosbuvir-velpatasvir for 12 weeks in all HCV genotypes without cirrhosis, with compensated cirrhosis, HCV/HIV coinfection, and in decompensated cirrhosis with ribavirin or for 24 weeks in patients with decompensated cirrhosis who cannot tolerate ribavirin[6,13].

Ledipasvir/sofosbuvir (Harvoni®)

Like sofosbuvir/velpatasvir, the ledipasvir/sofosbuvir combination offers a single-tablet, once daily regimen, requires 12-weeks of treatment for most indications, and is safe and effective in genotype 1 patients with decompensated cirrhosis (with ribavirin). It is limited however in coverage to only genotypes 1, 4, 5, and 6 without cirrhosis, with compensated cirrhosis or with decompensated cirrhosis. Ledipasvir/sofosbuvir offers an 8-week treatment course for genotype 1a patients who are HCV treatment-naïve, not African-American, non-cirrhotic, and whose HCV RNA level is <6 million IU/mL[11]. When these eligibility criteria are met, ledipasvir/sofosbuvir becomes an attractive, cost-effective option for IHS facilities although it has a lower level of recommendation for use by guidelines. Notably, other approved patient indications unique to ledipasvir/sofosbuvir include pediatric patients (≥12 years of age or weighing ≥35 kg with genotypes 1, 4, 5 and 6 without cirrhosis or with compensated cirrhosis) and liver transplant recipients (genotypes 1 and 4, without cirrhosis or with compensated cirrhosis in combination with ribavirin). Due to the shared sofosbuvir component, most other characteristics of ledipasvir/sofosbuvir are similar to sofosbuvir/velpatasvir.

Findings:

The availability of several highly efficacious and simplified pharmacotherapeutic options now on the National Core Formulary allow for routine treatment of the majority of patients chronically infected with HCV in the IHS population. Comprehensive HCV screening and treatment is broadly encouraged to reduce the burden of preventable morbidity and mortality from this prevalent disease. Resources available to IHS clinicians for HCV management include the IHS HCV ECHO program and Hepatitis C Online, a CDC-funded comprehensive online resource for HCV medications, their profiles (indications, dosing characteristics, interactions) and respective clinical trial outcomes.

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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