DAKLINZA / SOVALDI
(daclatasvir / sofosbuvir)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Hepatitis C is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. Most people infected with hepatitis C virus (HCV) have no symptoms of the disease until liver damage becomes apparent, which may take several years. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections or liver cancer (1).

Daclatasvir in combination with sofosbuvir is the first all oral 12-week regimen specifically for the treatment of hepatitis C genotype 3. Clinical trial tested a 12-week, ribavirin-free regimen and resulted in sustained virologic response (SVR12) in 98% of treatment-naïve and 92% of treatment-experienced genotype 3 with non-cirrhotic patients. Approximately 10% of HCV patients in the U.S. have genotype 3 (1).

Regulatory Status

FDA-approved indications:
Daklinza is a hepatitis C virus (HCV) NS5A inhibitor indicated for use with sofosbuvir for the treatment of chronic HCV genotype 3 infection (2).

Sovaldi is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen (3).

Limitations of Use:
Daklinza
Sustained virologic response (SVR) rates are reduced in patients with cirrhosis (2).

Off-Label Uses:
Daclatasvir in combination with sofosbuvir for the treatment of HCV genotype 1 infection can be recommended based on data from the phase III ALLY-2 trial, which assessed the efficacy and safety of daclatasivr and sofosbuvir for 12 weeks in patients. Cohort studies of a compassionate use program in Europe suggest that patients with cirrhosis may benefit from extension of therapy with daclatasvir and sofosbuvir to 24 weeks, with or without RBV (4).

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Daclatasvir with sofosbuvir for 12 weeks was approved by the FDA for the treatment of HCV genotype 3 infection in patients without and with cirrhosis. Although daclatasvir with sofosbuvir was not approved for the treatment of HCV genotype 2 infection, daclatasvir maintains adequate activity against HCV genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 polymorphism (4).

Daklinza is contraindicated in combination with drugs that strongly induce CYP3A and may lead to lower exposure and loss of efficacy (2).

Safety and effectiveness of Daklinza and Sovaldi in pediatric patients younger than 18 years of age have not been established (2, 3).

Summary

Daclatasvir in combination with sofosbuvir; is the first all oral 12-week regimen specifically for the treatment of hepatitis C genotype 3. Clinical trial tested a 12-week, ribavirin-free regimen and resulted in sustained virologic response (SVR12) in 98% of treatment-naïve and 92% of treatment-experienced genotype 3 with non-cirrhotic patients. Daklinza in combination with sofosbuvir with or without ribavirin can be used in the treatment of hepatitis C genotype1 and 2. Safety and effectiveness of Daklinza and Sovaldi in pediatric patients younger than 18 years of age have not been established (1-4).

Daklinza used in combination with Sovaldi may be considered **medically necessary** in patients 18 years of age or older with chronic Hepatitis C (required documented viral load (HCV RNA) at least 6 months prior to request for treatment) in patients with genotype 1 with or without cirrhosis that have had inadequate response, intolerance, or contraindication to Harvoni therapy; in patients with genotype 2 with or without cirrhosis that have had inadequate response, intolerance, or contraindication to Sovaldi and ribavirin therapy; in patients with genotype 3 with or without cirrhosis; patient does not have decompensated liver disease, used in combination with Sovaldi, and must be prescribed by a board-certified gastroenterologist, hepatologist, oncologist, or infectious disease specialist; absence of severe renal impairment (eGFR less than 30 ml/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis; has not had a liver transplant or is treatment naïve post-transplant and with no history of alcohol and/or substance abuse in the past 6 months; when combined with ribavirin then absence of significant or unstable cardiac disease, neither the patient nor the partner of the patient is pregnant, and if patient or their

partner are of child bearing age, the patient has been or will be instructed to practice effective contraception during therapy and for 6 months after stopping ribavirin therapy.

Daklinza used in combination with Sovaldi is considered i**nvestigational** for patients that are under 18 years of age and for patients that do not meet the criteria for medical necessity.

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Daklinza when taken in combination with Sovaldi while maintaining optimal therapeutic outcomes.

References

1. FDA News Release. FDA approves new treatment for chronic hepatitis C genotype 3 infections. July 24, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455888.htm
2. Daklinza [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; July 2015
3. Sovaldi [package insert]. Foster City, CA: Gilead Sciences, Inc; August 2015.
4. AASLD and IDSA: Recommendations for Testing, Managing, and Treating Hepatitis C; June 2015. www.hcvguidelines.org