Medical Policy

BlueCross BlueShield of Kansas
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Title: Hepatitis C First Generation Agents - Through Preferred Agent

See also:
- *Hepatitis B / Hepatitis C Peg-interferon – Through Preferred Agent(s)*
- *Hepatitis C Second Generation Antivirals – Through Preferred Agent(s)*

➢ **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6329KS-SOVA.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

Professional
Original Effective Date: February 24, 2015
Revision Date(s): February 24, 2015; September 1, 2015, January 1, 2016; March 21, 2016; June 1, 2016; September 1, 2016; November 1, 2016; May 15, 2017,
Current Effective Date: May 15, 2017

Institutional
Original Effective Date: February 24, 2015
Revision Date(s): February 24, 2015; September 1, 2015, January 1, 2016; March 21, 2016; June 1, 2016; September 1, 2016; November 1, 2016; May 15, 2017
Current Effective Date: May 15, 2017

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

DESCRIPTION

The intent of the Hepatitis C First Generation Prior Authorization (PA) program is to appropriately select patients for therapy according to the Food and Drug Administration (FDA) approved product labeling and/or clinical guidelines and/or clinical studies. If the client has preferred agent(s), a preferred agent may be approved for use once all criteria have been met; a non-preferred agent may be approved if the patient is currently treated with the non-preferred agent or the prescriber has provided documentation in support of use of the non-preferred agent over the preferred agent.

Target Agents

Preferred Agents	Non-preferred Agent
Sovaldi® (sofosbuvir) (preferred for genotype 1, 2, 3, and 4 with hepatocellular carcinoma and pediatric patients with genotype 2 or 3)	**Daklinza**™ (daclatasvir) **Olysio**® (simeprevir)

FDA Approved Indications and Dosage

Medication	Indications	Dose and Interval
Daklinza (daclatasvir)	Treatment of chronic hepatitis C genotype 1 or 3 in combination with sofosbuvir with or without ribavirin	60 mg tablet taken orally once daily^ with or without food in combination with sofosbuvir with or without ribavirin
Olysio (simeprevir)*	Treatment of adults with chronic hepatitis C virus (HCV) infection ▪ In combination with sofosbuvir in patients with HCV genotype 1 without cirrhosis or with compensated cirrhosis ▪ In combination with peg-interferon and ribavirin in patients with HCV genotype 1 or 4 without cirrhosis or with compensated cirrhosis (Child-Pugh A)	150 mg once daily
Sovaldi (sofosbuvir)	▪ Treatment of adults with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection ▪ Treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 2 or 3 infection including those who are treatment-naïve or treatment experience without cirrhosis or with compensated cirrhosis (Child-Pugh A)	400 mg tablet taken once daily with or without food. Most patients will be on therapy for 12 to 24 weeks. Those with hepatocellular carcinoma may require up to 48 weeks.

^Daclatasvir dose modification: Reduce dosage to 30 mg once daily with strong CYP3A inhibitors and increase dosage to 90 mg once daily with moderate CYP3A inducers

*Olysio limitations of use:

- Efficacy of Olysio in combination with peg-interferon and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism
- Olysio is not recommended in patients who have previously failed therapy with a treatment regimen that included Olysio or other HCV protease inhibitors

POLICY

Prior Authorization Criteria for Approval

A. **Sovaldi** (sofosbuvir) will be approved when ALL of the following are met:
   1. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, or 4 or hepatocellular carcinoma secondary to chronic hepatitis C genotype 1, 2, 3, or 4
      AND
   2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
      AND
   3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist.
      AND
   4. The patient does not have any FDA labeled contraindications to the requested agent
      AND
   5. ONE of the following:
      a. The patient is treatment naïve
         OR
      b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin
      AND
   6. The dose is within the FDA labeled dose
      AND
   7. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 1, 2, 3 and 4 (FDA labeling)

Length of Approval: Up to the duration of treatment as determined in Table 1, 2, 3 and 4

Prior Authorization Criteria for Approval

B. **Daklinza** (daclatasvir) will be approved when ALL of the following are met:
   1. The patient has a diagnosis of chronic hepatitis C genotype 1 or 3
      AND
   2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
      AND
   3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist
      AND
   4. The patient does not have any FDA labeled contraindications to the requested agent
      AND
   5. ONE of the following:
      a. The patient is treatment naïve
         OR
      b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin
      AND
   6. The dose is within ONE of the following FDA labeled doses:
      a. Daklinza 30mg (1 tablet) daily and the patient is also receiving a strong CYP3A inhibitor
         OR
      b. Daklinza 60 mg (1 tablet) daily
         OR
      c. Daklinza 90 mg (1 tablet) daily and the patient is also receiving a moderate CYP3A inducer
      AND
   7. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 2 (FDA labeling)

Length of Approval: Up to the duration of treatment determined in Table 3

Prior Authorization Criteria for Approval

C. **Olysio** (simeprevir) will be approved when ALL of the following are met:
1. The patient has a diagnosis of chronic hepatitis C genotype 1 or 4
   AND
2. If requesting Olysio to be used with peg-interferon and ribavirin for genotype 1a, the patient does not have NS3 Q80K polymorphism
   AND
3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent
   AND
4. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist
   AND
5. The patient does not have any FDA labeled contraindications to the requested agent
   AND
6. ONE of the following:
   a. The patient is treatment naïve
      OR
   b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin
   AND
7. The dose is within the FDA labeled dose
   AND
8. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 4 and 5 (FDA labeling)

Length of Approval: Up to the duration of treatment as determined in Table 4 and 5

Prior Authorization Criteria for Approval

D. **Non-preferred agent(s)** will be approved when the drug specific criteria above and ONE of the following additional criteria are met:
   1. The patient is currently being treated with the non-preferred agent
      OR
   2. The patient has an FDA labeled contraindication or hypersensitivity to the preferred agent(s)
      OR
   3. The prescriber has submitted documentation in support of the use of the non-preferred agent over the preferred agent(s)

Table 1: Sovaldi and Ribavirin with or without Peg-interferon Treatment Recommendations Based on FDA Labeling

Adult Patient population*	Treatment	Duration of therapy
Genotype 1 or 4	Sovaldi + Peg-interferon + ribavirin	12 weeks
Genotype 1 (interferon ineligible±)	Sovaldi + ribavirin	24 weeks
Genotype 2	Sovaldi + ribavirin	12 weeks
Genotype 3	Sovaldi + ribavirin	24 weeks
1-4 with hepatocellular carcinoma awaiting liver transplantation	Sovaldi + ribavirin	Up to 48 weeks

Table 2: Sovaldi and Ribavirin with or without Peg-interferon Treatment Recommendations Based on FDA Labeling

Genotype	Pediatric Patient population ≥ 12 years of age and older Weighing at Least 35 Kg*	Treatment	Duration of therapy
2	Treatment-naïve and treatment experienced¥ without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sovaldi + ribavirin	12 weeks
3	Treatment-naïve and treatment experienced¥ without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Sovaldi + ribavirin	24 weeks

Table 3: Sovaldi and Daklinza Combination Treatment Recommendations Based On FDA Labeling

Genotype	Patient population*	Treatment	Duration of therapy
1	Without cirrhosis	Daklinza + Sovaldi	12 weeks
	Compensated (Child-Pugh A) cirrhosis	Daklinza + Sovaldi	12 weeks
	Decompensated (Child-Pugh B or C) cirrhosis	Daklinza + Sovaldi + ribavirin	12 weeks
	Post-transplant	Daklinza + Sovaldi + ribavirin	12 weeks
3	Without cirrhosis	Daklinza + Sovaldi	12 weeks
	Compensated (Child-Pugh A) cirrhosis	Daklinza + Sovaldi + ribavirin	12 weeks
	Decompensated (Child-Pugh B or C) cirrhosis	Daklinza + Sovaldi + ribavirin	12 weeks
	Post-transplant	Daklinza + Sovaldi + ribavirin	12 weeks

*Includes patients with HCV/HIV co-infection
¥Treatment-experienced patients who have failed an interferon based regimen with or without ribavirin
±Interferon ineligible is defined as one or more of the following:

- Intolerance* to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/µL, a baseline platelet count below 90,000/µL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

*Intolerance is defined by Prime as intolerance to the drug and/or excipients, not the route of administration including patients who have previously discontinued therapy with IFN due to adverse events (e.g. hypersensitivity, anaphylaxis, severe rash, severe anemia, etc.).

Table 4: Olysio and Sovaldi Combination Therapy Treatment Recommendations Based on FDA Labeling

Genotype and Patient Population	Treatment regimen and duration
Genotype 1 treatment naïve and treatment-experienced* patients without Cirrhosis	12 weeks of Olysio + Sovaldi
Genotype 1 treatment naïve and treatment-experienced* patients with compensated Cirrhosis (Child-Pugh A)	24 weeks of Olysio + Sovaldi

*Treatment-experienced patients include prior relapsers, partial responders and prior null responders who failed peg-interferon plus ribavirin and peg-interferon intolerant patients

Table 5: Olysio, Peg-interferon (PEG-IFN), and Ribavirin Treatment Recommendations based on FDA Labeling

Genotype	Patient population	Treatment regimen	Duration of therapy
1 or 4	Treatment naïve and prior relapsers* HCV monoinfected patients without cirrhosis or with compensated cirrhosis (Child-Pugh A)	Olysio + PEG-IFN + RBV	Olysio: 12 weeks PEG-IFN: 24 weeks
	Treatment naïve and prior relapsers* with HCV/HIV co-infected patients without cirrhosis	Olysio + PEG-IFN + RBV	Olysio:12 weeks PEG-IFN: 24 weeks
	Treatment naïve and prior relapsers* with HCV/HIV co-infection with compensated cirrhosis (Child-Pugh A)	Olysio + PEG-IFN + RBV	Olysio: 12 weeks PEG-IFN: 48 weeks
	Prior non-responders (including partial± and null responders^) without cirrhosis or with compensated cirrhosis (Child-Pugh A) and with or without HIV co-infection	Olysio + PEG-IFN + RBV	Olysio: 12 weeks PEG-IFN: 48 weeks

*Prior relapse: HCV RNA not detected at the end of prior IFN based therapy and HCV RNA detected during follow up.
± Prior partial responder: Prior on-treatment ≥ 2 log10 IU/mL reduction in HCV RNA from baseline at week 12 and HCV RNA detected at the end of prior IFN based therapy.
^ Prior null responder: Prior on treatment < 2 log 10 reduction in HCV RNA from baseline at week 12 during prior IFN based therapy.

Agent(s)	Contraindication(s)
Daklinza (daclatasvir)	Use in combination with drugs that strongly induce CPY3A due to decreased or loss of efficacy with Daklinza
Olysio (simeprevir)	Because Olysio is used only in combination with other antiviral drugs (including peg-interferon and ribavirin) for the treatment of chronic HCV infection, the contraindications to other drugs also apply to the combination regimen
Sovaldi (sofosbuvir)	Pregnancy and for men whose partners are pregnant (ribavirin) and any contraindications that apply to peginterferon if agent will be used in combination with peginterferon

RATIONALE

Disease Background[4,5]

Hepatitis C is an infection of the liver caused by the Hepatitis C virus (HCV) and is one of the leading causes of chronic liver disease in the United States. According to the Centers for Disease Control and Prevention (CDC), there were an estimated 3.5 million people infected with hepatitis C as of 2015. Hepatitis C infection can either be acute or chronic. Acute HCV infection is defined as presenting within 6 months following exposure to the virus. The infection is defined as chronic if the virus is present beyond 6 months following exposure. 70% to 80% of those infected with HCV will go on to develop chronic HCV infection.

Persons at high risk for contracting HCV infection include intravenous drug users, recipients of donated blood, blood products, and organs (now rare in the United States due to stringent blood screening), babies born to HCV infected mothers, and persons with HIV infection.

Hepatitis C infection is asymptomatic in the early stages of the disease. However, with disease progression, patients may develop mild to severe chronic liver disease including cirrhosis and liver cancer. The goal of therapy is to eradicate the virus and prevent liver damage including cirrhosis. Direct acting antivirals (DAAs) are currently the mainstay of treatment for chronic HCV infection. Certain DAAs may be used as monotherapy while others require use in combination with other agents including peg-interferon, ribavirin and other DAAs.

The American Association of the Study of Liver Disease (AASLD) and the Infectious Disease Society of America (IDSA) have developed guidelines to aid in the management of hepatitis C. The guidelines address issues ranging from testing and linkage to care to the optimal treatment regimen based on patient situations.

AASLD/IDSA guidelines on when and in whom to treat[5]

The goal of therapy is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure. According to the AASLD/IDSA guidelines, treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Treatment should be initiated early because delaying therapy may decrease the benefits of eradicating the hepatitis C viral infection.

AASLD recommends awaiting availability of pangenotypic agents for the management of patients with mixed genotypes. Patients who are co-infected with HCV and either hepatitis B or HIV should be treated as those mono-infected with HCV.

Daclatasvir [1]

Efficacy of daclatasvir in combination with sofosbuvir with or without ribavirin for patients with HCV genotype 1 was evaluated in the ALLY-1 and ALLY-2 trials. ALLY-1, an open-label trial, included patients with cirrhosis, recurrent infection, and/or history of liver transplantation. All subjects in the ALLY-1 trial received daclatasvir in combination with sofosbuvir and ribavirin for 12 weeks. The primary outcome was sustained virologic response at 12 weeks following treatment (SVR12) which ranged from 76% to 100% as outlined in Table 1 below.

Table 1: ALLY-1 SVR12 in Genotype 1 Subjects

Treatment Outcomes	Child-Pugh A, B, or C Cirrhosis n=45	Post-Liver Transplant n=41
SVR12		
Genotype 1	82% (37/45)	95% (39/41)
Child-Pugh A	91% (10/11)	-
Child-Pugh B	92% (22/24)	-
Child-Pugh C	50% (5/10)	-
Genotype 1a	76% (26/34)	97% (30/31)
Genotype 1b	100% (11/11)	90% (9/10)

ALLY-2 trial was an open-label trial evaluating the efficacy of daclatasvir in combination with sofosbuvir in patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6. Although this trial included patients with HCV genotype 1 to 6, this combination is FDA approved only for treatment of HCV genotype 1 and 3 therefore, clinical trial data for other genotypes will not be discussed here. Subjects with genotype 1 enrolled in the ALLY-2 trial received daclatasvir plus sofosbuvir for 12 weeks. The primary outcome, overall SVR12, was 97% in genotype 1 patients. Patients with HCV genotype 1 and cirrhosis had a lower SVR12 (91%) as compared to those without cirrhosis (98%). SVR12 in genotype 3 patients was 100%.

Efficacy and safety of daclatasvir in combination with sofosbuvir for HCF genotype 3 was also evaluated in (the ALLY-3 trial). The study enrolled 152 subjects with chronic hepatitis C genotype 3 infection and compensated liver disease. 101 subjects were treatment naïve, 7 subjects had been previously treated with a sofosbuvir regimen, and 2 subjects had previously received treatment with an investigational cyclophilin inhibitor. Subjects with previous exposure to an NS5A inhibitor (e.g. daclatasvir, ledipasvir, or ombitasvir) were excluded from the trial.

The primary end point, SVR12, was 92% to 98% and 58% to 69% for patients without cirrhosis and for those with cirrhosis respectively. Relapse rates following completion of treatment were 9% to 14%.

The most common adverse events associated with daclatasvir were headache and fatigue when used in combination with sofosbuvir. Headache, anemia, fatigue, and nausea were the most common adverse events observed when daclatasvir was used combination with sofosbuvir and ribavirin.

Simeprevir[2,4]

Simeprevir is a HCV NS3/4A protease inhibitor. It is indicated for use in combination with sofosbuvir or in combination with ribavirin and peg-interferon (triple therapy). AASLD/IDSA no longer recommend use of simeprevir in combination with ribavirin and peg-interferon for genotype 1 patients due to low efficacy and high potential for side effects.

The safety profile of simeprevir is similar if not improved compared to other agents in this class. The most common adverse events in treated patients (in combination with peginterferon and ribavirin) (>20%) and occurring with at least 3% higher frequency compared to subjects receiving placebo (also in combination with peginterferon and ribavirin) include rash (including photosensitivity), pruritus and nausea. Serious symptomatic bradycardia may occur when simeprevir is administered in combination with sofosbuvir and amiodarone.

Sofosbuvir[3]
Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor. It is indicated for use in combination with other DAAs including daclatasvir and simeprevir. It may also be used in combination with peg-interferon and ribavirin. The efficacy of sofosbuvir (SVR12) is dependent on the combination regimen in which it is used, the patient's genotype, and patient's treatment history. To date, sofosbuvir is the only oral DAA indicated for treatment of patients with hepatocellular carcinoma secondary to chronic HCV infection.

The most common adverse events of sofosbuvir when used with ribavirin include fatigue headache and insomnia. Nausea, insomnia, and anemia were the most common adverse events when sofosbuvir was used in combination with ribavirin and peg-interferon.

Risk of Hepatitis B infection reactivation with HCV Direct Acting Antivirals[6]
In October of 2016, the FDA issued a safety alert concerning risk of reactivation of hepatitis B viral (HBV) infection in patients treated with HCV direct acting antivirals (DAA). At the time of the alert, the FDA had identified 24 cases of HBV infection reactivation in patients who had been treated with a HCV DAA. In a few of these cases, the HBV reactivation resulted in serious liver problems or death. As a result, the FDA has required labeling for all HCV DAAs to include a boxed warning for HBV infection reactivation. In addition, the FDA has recommended that all patients be screened for evidence of current or prior HBV infection before starting treatment with HCV DAAs and be monitored for HBV reactivation during and after treatment with a HCV DAA.

REVISIONS	
02-24-2015	Policy added to the bcbsks.com web site.
09-01-2015	Policy added to the bcbsks.com web site on 08-25-2015 and effective 09-01-2015.
	Description section updated
	In Policy section: ▪ In Initial Evaluation Item 4 a removed "(as determined by client)" ▪ In Length of Approval add "Up to the duration" to read, "Up to the duration as determined in Table 3…"
	Rationale section updated
	References updated
01-01-2016	Policy published 12-30-2015. Policy effective 01-01-2016.
	In Policy Title removed "[sofosbuvir]" and added " and Daklinza™" to read "Hepatitis C - Sovaldi® and Daklinza™ (2015) - Through Preferred Agent(s)"
	Description section updated to include ▪ Adding as Preferred Agents: Daklinza™ (daclatasvir) and Pegasys® (peg-interferon alfa-2a) ▪ Added as a Non-preferred Agent: Pegintron® (peg-interferon alfa-2b) ▪ Added Daklinza to FDA Approved Indications and Dosage chart
	In Policy section: ▪ In Item A 1 added "or hepatocellular carcinoma secondary to chronic hepatitis C infection" to read, "The patient has a diagnosis of chronic hepatitis C infection or hepatocellular carcinoma secondary to chronic hepatitis C infection" ▪ In Item A 2 added "The hepatitis C infection has been" to read, "The hepatitis C infection has been confirmed by serological markers" ▪ In Item A 3 added Harvoni, Technivie and Viekira to read, "The patient will NOT be receiving Harvoni (sofosbuvir/ledipasvir), Incivek (telaprevir), Olysio (simeprevir), Technivie (ombitasvir/paritaprevir/ ritonavir), Victrelis (boceprevir) or Viekira

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	(ombitasvir/paritaprevir/ritonavir + dasabuvir) concomitantly with sofosbuvir" ▪ In Item A 4 added Daklinza, Harvoni, Sovaldi, Viekira, and Technivie to read, "The patient has NOT been previously treated with Daklinza (daclatasvir), Harvoni (sofosbuvir/ledipasvir), Sovaldi (sofosbuvir), Viekira (ombitasvir/paritaprevir/ ritonavir + dasabuvir) or Technivie (ombitasvir/paritaprevir/ritonavir) as a component of any treatment regimen" ▪ In Item A 7 added "and length of therapy" to read "Sofosbuvir will be used in a combination antiviral treatment regimen and length of therapy supported by FDA approved labeling or the AASLD guidelines ▪ In Item A 12 removed "sofosbuvir" and added "Sovaldi" and "a. The requested dose is less than or equal to 60 mg (one tablet) daily OR BOTH of the following: i. The requested dose is 90 mg daily (three 30 mg tablets) AND ii. The patient is concurrently treated with a moderate CYP3A4 inducer" to read, "The dose of Sovaldi sofosbuvir is within the FDA labeled dosage (400 mg daily) AND a. The requested dose is less than or equal to 60 mg (one tablet) daily OR BOTH of the following: i. The requested dose is 90 mg daily (three 30 mg tablets) AND ii. The patient is concurrently treated with a moderate CYP3A4 inducer" ▪ In Item B removed "(TRIPLE THERAPY)" and "for the preferred peginterferon listed" and added "agent(s) (oral agent(s)) and/or" to read, " Initial Evaluation – Non-preferred agent(s) (oral agent(s)) and/or peg-interferon will be approved when the criteria above are met AND ONE of the following is met:" ▪ In Item B a added "oral" and "and/or peg-interferon" to read "The patient is currently being treated with the non-preferred oral agent(s) and/or peg-interferon" ▪ In Item 2 added "BOTH of the following: a. If requesting a non-preferred peg-interferon, ONE of the following:" and "If requesting a non-preferred oral agent, the patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred oral agent" to read "2. BOTH of the following: a. If requesting a non-preferred peg-interferon, ONE of the following: i. The patient has a history of a trial of the preferred peg-interferon OR ii. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred peginterferon, ORpeg-interferon agent AND b. If requesting a non-preferred oral agent, the patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred oral agent" ▪ In Item 3 added "oral agent and/or non-preferred" to read, "The prescriber has submitted documentation in support of the use of the non-preferred oral agent and/or non-preferred peg-interferon, for the intended diagnosis" ▪ In Length of Approval "removed (Sovaldi [sofosbuvir]) to read, "Up to the duration as determined in Table 3 below based on regimen and genotype." ▪ Updated FDA approved and/or AASLD/IDSA recommended antiviral regimens table, which includes Duration of therapy information ▪ Added Contraindications table.
	Rationale section updated
	References updated
03-21-2016	In Title section removed "(2015)"
	Description section updated to include updates to the FDA Approved Indications and Dosage chart
	In Policy section: <u>Initial Evaluation – Sovaldi…</u> ▪ In Item A 3 added "or Zepatier (elbasvir/grazoprevir)" to read "The patient will NOT be

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	receiving Harvoni (sofosbuvir/ledipasvir), Incivek (telaprevir), Olysio (simeprevir), Technivie (ombitasvir/paritaprevir/ritonavir), Victrelis (boceprevir), Viekira (ombitasvir/paritaprevir/ritonavir + dasabuvir) or Zepatier (elbasvir/grazoprevir) concomitantly with sofosbuvir" ▪ In Item A 4 added "or Zepatier (elbasvir/grazoprevir)" to read "The patient has NOT been previously treated with Daklinza (daclatasvir), Harvoni (sofosbuvir/ledipasvir), Sovaldi (sofosbuvir), Viekira (ombitasvir/paritaprevir/ritonavir + dasabuvir), Technivie (ombitasvir/paritaprevir/ritonavir), or Zepatier (elbasvir/grazoprevir) as a component of any treatment regimen" ▪ In Item 5 added "1 or" to read "If requesting Sovaldi in combination with Daklinza, the patient has chronic hepatitis C genotype 1 or 3 infection' ▪ In Item 7 added "and/" to read "Sofosbuvir will be used in a combination antiviral treatment regimen and length of therapy supported by FDA approved labeling and/or the AASLD guidelines" ▪ Corrected Item 13 adding "If requesting Daklinza (daclatasvir) ONE of the following:", which was erroneously left of the previous revision. <u>In Initial Evaluation – Non-preferred agents:</u> ▪ In Length of Approval added "4, or 5" to read "Up to the duration as determined in Table 3, 4, or 5 below based on regimen and genotype." ▪ Updated Table 3 revising title from "FDA approved and/or AASLD/IDSA recommended antiviral regimens" to "FDA Approved Sovaldi plus ribavirin with or without peginterferon antiviral regimens" ▪ Added Table 4 "FDA approved Sovaldi plus Daklinza antiviral regimens" ▪ Added Table 5 "AASLD/IDSA recommended Sovaldi based antiviral regimens"
	Rationale section updated
	References updated
06-01-2016	Published 05-25-2016. Effective 06-01-2016.
	In Policy section: ▪ In Item A removed the following criteria: "ONE of the following: a. The patient has a METAVIR score of ≥2 OR b. The patient has a Ishak score ≥3 OR c. The patient has a Fibroscan score of ≥7.65 kPa OR d. The patient has radiological imaging consistent with fibrosis and/or cirrhosis (e.g. portal hypertension, esophageal varices) OR e. The patient has type 2 or 3 mixed cryoglobulinemia with end-organ manifestations (e.g. vasculitis) OR f. The patient has proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis OR g. The patient is currently awaiting liver transplant OR h. The patient is post-liver transplant OR i. The patient is co-infected with HIV-1" Updated Table 3 FDA Approved Sovaldi plus ribavirin with or without peginterferon antiviral regimens.
	Rationale section updated to include updating the AASLD recommendations removing priority treatment criteria.
09-01-2016	Title changed to "Hepatitis C First Generation - Through Preferred Agent(s)" from "Hepatitis C First Generation - Sovaldi and Daklinza"
	Description section updated ▪ Added Olysio (simeprevir) and removed of Pegasys (peg-interferon alfa-2a) and Pegintron (peg-interferon alfa-2b) from the Target Drugs list. See policy Hepatitis B / Hepatitis C Peg-interferon medical policy for Peg-interferon criteria.

REVISIONS	
	▪ FDA Approved Indications and Dosage chart updated accordingly.
	In Policy section: ▪ In Item A removed "Initial Evaluation", "Pegylated Interferon and Saklinza (declatasvir)" and added "will be approved when ALL of the following are met" to read "Sovaldi (sofosbuvir) will be approved when ALL of the following are met:" ▪ In Item A 1 removed "infection" and added "genotype 1, 2, 3, or 4" to read "The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, or 4 or hepatocellular carcinoma secondary to chronic hepatitis C genotype 1, 2, 3, or 4" ▪ In Item A 2 removed "If able, the prescriber will provide an SVR post treatment week 12" and added" requested" to read "The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist." ▪ In Item A 3 removed " sofosbuvir or the other agents used in the combination therapy" and added "the requested agent" to read "The patient does not have any FDA labeled contraindications to the requested agent" ▪ Added: "4. ONE of the following: a. The patient is treatment naïve OR b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin AND 5. The dose is within the FDA labeled dose AND 6. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 1,2, and 3 (FDA labeling)" ▪ Added "Length of Approval: Up to the duration of treatment as determined in Table 1, 2, and 3" ▪ Removed the following criteria : • "The hepatitis C infection has been confirmed by serological markers" • "The patient will NOT be receiving Harvoni (sofosbuvir/ledipasvir), Incivek (telaprevir), Olysio (simeprevir), Technivie (ombitasvir/paritaprevir/ritonavir), Victrelis (boceprevir), Viekira (ombitasvir/paritaprevir/ritonavir + dasabuvir) or Zepatier (elbasvir/grazoprevir) concomitantly with sofosbuvir" • "The patient has NOT been previously treated with Daklinza (daclatasvir), Harvoni (sofosbuvir/ledipasvir), Sovaldi (sofosbuvir), Viekira (ombitasvir/paritaprevir/ritonavir + dasabuvir), Technivie (ombitasvir/paritaprevir/ritonavir), or Zepatier (elbasvir/grazoprevir) as a component of any treatment regimen" • "If requesting Sovaldi in combination with Daklinza, the patient has chronic hepatitis C genotype 1 or 3 infection" • "Sofosbuvir will be used in a combination antiviral treatment regimen and length of therapy supported by FDA approved labeling and/or the AASLD guidelines" • "The patient is not co-infected with chronic hepatitis B" • "If the patient has hepatocellular carcinoma the following are met: The patient has either a single tumor 5 cm or less in diameter OR The patient has up to 3 tumors with each being 3 cm or less in diameter AND The patient has NO extrahepatic manifestations of cancer or evidence of vascular invasion of tumor" • "The dose of Sovaldi is within the FDA labeled dosage (400 mg daily)" • "If requesting Daklinza (daclatasvir) ONE of the following: The requested dose is less than or equal to 60 mg (one tablet) daily OR BOTH of the following: The requested dose is 90 mg daily (three 30 mg tablets) AND The patient is concurrently treated with a moderate CYP3A4 inducer" ▪ Added Item B new criteria for Daklinza

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	"B. Daklinza (daclatasvir) will be approved when ALL of the following are met: 1. The patient has a diagnosis of chronic hepatitis C genotype 1 or 3 AND 2. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist AND 3. The patient does not have any FDA labeled contraindications to the requested agent AND 4. ONE of the following: a. The patient is treatment naïve OR b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin AND 5. The dose is within ONE of the following FDA labeled doses: a. Daklinza 30mg (1 tablet) daily and the patient is also receiving a strong CYP3A inhibitor OR b. Daklinza 60 mg (1 tablet) daily OR c. Daklinza 90 mg (1 tablet) daily and the patient is also receiving a moderate CYP3A inducer AND 6. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 2 (FDA labeling) Length of Approval: Up to the duration of treatment determined in Table 2" ▪ Added Item C criteria for Olysio "C. Olysio (simeprevir) will be approved when ALL of the following are met: 1. The patient has a diagnosis of chronic hepatitis C genotype 1 or 4 AND 2. If requesting Olysio to be used with peg-interferon and ribavirin for genotype 1a, the patient does not have NS3 Q80K polymorphism AND 3. The requested agent is being prescribed by a specialist (e.g. gastroenterologist, hepatologist, infectious disease) or in consultation with a specialist AND 4. The patient does not have any FDA labeled contraindications to the requested agent AND 5. ONE of the following: a. The patient is treatment naïve OR b. The patient was previously treated (i.e. treatment experienced) with ONLY peg-interferon and ribavirin AND 6. The dose is within the FDA labeled dose AND 7. The requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 3 and 4 (FDA labeling) Length of Approval: Up to the duration of treatment as determined in Table 3 and 4" ▪ In Item D removed "Initial Evaluation" and "(oral agent(s) and/or ;eg-interferon)" and added "drug specific" and "additional criteria are" to read "Non-preferred agent(s) will be approved when the drug specific criteria above and ONE of the following additional criteria are met:" ▪ In Item D 1 removed "oral" and "and/or peg-interferon" to read "The patient is currently being treated with the non-preferred agent" ▪ Added Item D 2 "The patient has an FDA labeled contraindication or hypersensitivity to the preferred agent(s)" ▪ In Item D 3 removed "oral" and "and/or non-preferred peg-interferon, for the intended diagnosis" and added "over the preferred agent(s)" to read "The prescriber has submitted documentation in support of the use of the non-preferred agent over the preferred agent(s)" ▪ In Item D removed "Length of Approval: Up to the duration as determined in Table 3, 4, or 5 below based on regimen and genotype." ▪ Updated Table 1 and Table 2 Titles ▪ Removed the Table titled "AASLD/IDSA recommended Sovaldi based antiviral regimens"

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	▪ Added "Table 3: Olysio and Sovaldi Combination Therapy Treatment Recommendations Based on FDA Labeling" and "Table 4: Olysio, Peg-interferon (PEG-IFN), and Ribavirin Treatment Recommendations based on FDA Labeling" ▪ Updated the Contraindications table
	Rationale section updated
	References updated
11-01-2016	In Description section: ▪ In Target Drugs moved "Daklinza (daclatasvir)" from being a preferred agent to being a non-preferred agent.
05-15-2017	In Title section added "Agents" to read "Hepatitis C First Generation Agents – Through Preferred Agents"
	In Description section ▪ Updated Target Agents chart adding the following notation to the Preferred Agent Sovaldi "(preferred for genotype 1, 2, 3, and 4 with hepatocellular carcinoma and pediatric patients with genotype 2 or 3)" ▪ Updated the Sovaldi indications in the FDA Approved Indications and Dosage chart.
	In Policy section: ▪ In Items A 2, B 2, and C 3 added "The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection and will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent" ▪ In Item A 7 and Length of Approval added "and 4" to the Table listing ▪ In Item B Length of Approval revised "Table 2" to "Table 3" ▪ In Item C 8 and Length of Approval Revised "Table 3 and 4" to "Table 4 and 5" ▪ Updated Table 1 ▪ Added new Table 2 and re-numbered Tables accordingly
	Rationale section updated
	References updated

REFERENCES

1. Daklinza prescribing information. April 2016.
2. Olysio prescribing information. Jannsen. May 2016.
3. Sovaldi prescribing information. Gilead. April 2017.
4. AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Testing Hepatitis C. Available at www.hcvguidelines.org . Accessed June 2016.
5. The center for Disease Control and Prevention. Viral Hepatitis Statistics and Surveillance. Available at http://www.cdc.gov/hepatitis/statistics Accessed June 2016.
6. Direct-Acting Antivirals for Hepatitis C : FDA Drug Safety Communication-Risk of Hepatitis B Reactivation. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm523690.htm Accessed November 2016.