Medical Policy

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Title: Hepatitis B / Oncology and Hepatitis C Agents (Pegasys®/Pegasys, Proclick®/peginterferon alfa-2a, PegIntron®/peginterferon alfa-2b, Incivek®™/telaprevir, Olysio™/ simeprevir, Sovaldi™/sofosbuvir, and Victrelis®™/boceprevir)

- **Prime Therapeutics will review Prior Authorization requests.**

Prior Authorization Forms:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth_6033KS_PegInterferon.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth_6187KS_Incivek_Victrelis.pdf
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth_6329KS_Sovaldi.pdf

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

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

Professional
Original Effective Date: January 1, 2012
Revision Date(s): March 28, 2012; July 1, 2012, January 1, 2013; January 1, 2014; February 10, 2014; April 22, 2014; June 15, 2014
Current Effective Date: June 15, 2014

Institutional
Original Effective Date: January 1, 2012
Revision Date(s): March 28, 2012; July 1, 2012; January 1, 2013; January 1, 2014; February 10, 2014; April 22, 2014; June 15, 2014
Current Effective Date: June 15, 2014

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I. HEPATITIS B / Oncology – Through Preferred Agent

DESCRIPTION

The intent of the Peginterferon Prior Authorization (PA) Criteria 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. The PA process will evaluate the use of peginterferon when there is supporting clinical evidence or prescriber-provided documentation supporting the unlabeled use. When criteria for use are met, the preferred agent, Pegasys, may be approved for use; use of the non-preferred peginterferon, PegIntron, will be evaluated if the prescriber indicates current use of PegIntron, or a request for PegIntron for:

A. chronic myelogenous leukemia or another oncology indication that is supported by compendia, or
B. a history of a trial and failure of, documented intolerance of, contraindication to, or hypersensitivity to the preferred interferon Pegasys.

Target Drugs

Preferred peginterferon	Non-Preferred peginterferon
Pegasys® (peginterferon alfa-2a)	PegIntron® (peginterferon alfa-2b)

FDA Approved Indications and Dosage[1,2]

Available Products	FDA Indication(s)	Dosage and Administration
Pegasys® / Pegasys® Proclick (peginterferon alfa-2a) subcutaneous injection	• Chronic, Active Hepatitis B (≥18 years) • Chronic Hepatitis C (≥18 years), monotherapy • Hepatitis C + HIV co-infection (≥18 years) monotherapy	• 180 mcg sc once weekly for 48 weeks
	• Chronic Hepatitis C (≥5 years), in combination with ribavirin	• 180 mcg sc once weekly and ribavirin 800-1200 mg daily depending on genotype and weight given in two divided doses for a total of up to 48 weeks • Pediatric dosing is 180 mcg/1.73 m^2 x BSA once weekly and 400-1200 mg daily of ribavirin in divided doses depending on weight for up to 48 weeks
	• Chronic Hepatitis C + HIV co-infection (≥18 years)in combination with ribavirin	• 180 mcg sc once weekly and ribavirin 800 mg daily given in two divided doses for a total of or 48 weeks regardless of genotype

Available Products	FDA Indication(s)	Dosage and Administration
PegIntron® (peginterferon alfa-2b) subcutaneous injection	• Chronic Hepatitis C (≥18 years), interferon-alpha naïve or prior treatment failure, monotherapy	• 1 mcg/kg/week sc for up to 1 year administered on the same day of the week
	• Chronic Hepatitis C in patients (age 3-17 years), interferon-alpha naïve or prior treatment failure, in combination with ribavirin	• 60 mcg/m^2/week sc in combination with 15 mg/kg/day of ribavirin orally in two divided doses for up to 24 weeks (genotypes 2, 3) or up to 48 weeks (genotype 1)
	• Chronic Hepatitis C (≥18 years), interferon-alpha naïve or prior treatment failure, in combination with ribavirin.	• 1.5 mcg/kg/week sc in combination with 800 to 1400 mg of ribavirin (based on body weight) for 24 weeks (genotypes 2, 3) or 48 weeks (genotype 1)

sc–subcutaneously; po-orally

POLICY

Prior Authorization Criteria for Approval

A. Pegasys® or PegIntron® will be approved when the following are met:
1. The patient does not have any FDA labeled contraindications to therapy
   AND
2. ONE of the following:
   a. Peginterferon is being prescribed for the treatment of chronic myelogenous leukemia (CML)
      OR
   b. The use of the requested agent is for an oncology indication that is supported by compendia (NCCN Compendium™ level of evidence 1, 2A, or 2B, AHFS, DrugDex, Clinical Pharmacology) or the prescriber has submitted additional documentation supporting the requested therapeutic use

B. Pegasys® (for chronic hepatitis B infection) will be approved when the following are met:
1. The patient does not have any FDA labeled contraindications to therapy
   AND
2. The patient has not been administered peginterferon for more than 18 months of total therapy
   AND
3. Peginterferon is being prescribed for the treatment of chronic hepatitis B virus infection confirmed by serological markers

C. PegIntron® (for chronic hepatitis B infection) will be approved when the criteria for Pegasys listed above are met AND the following are met:

1. The patient does not have any FDA labeled contraindications to therapy
   AND
2. The patient is currently being treated with the non-preferred agent, PegIntron (peginterferon alfa-2b)
   OR
3. ONE of the following:
   a. The patient has a history of a trial and failure of the preferred peginterferon, Pegasys
      OR
   b. The patient has a contraindication to, intolerance of, or allergy to the preferred peginterferon, Pegasys
      OR
   c. The prescriber has submitted documentation in support of the use of the non-preferred peginterferon, PegIntron, for the intended diagnosis

Length of Approval:

- 18 months for confirmed hepatitis B virus infection
- Indefinite for treatment of CML or oncology indication as supported by compendia

II. HEPATITIS C AGENTS - Through Preferred Hepatitis C Agents
(Pegasys, PegIntron, Incivek, Olysio, Sovaldi, Victrelis)

DESCRIPTION
The intent of the Hepatitis C Agents (Pegasys, PegIntron, Incivek, Olysio, Sovaldi, and Victrelis) Prior Authorization (PA) Criteria 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. The oral agents Incivek, Olysio, Sovaldi, and Victrelis will not be approved as monotherapy; Incivek and Victrelis must be used in combination with peginterferon alfa and/or ribavirin. The PA process will evaluate the use of these hepatitis C agents when there is supporting clinical evidence or prescriber-provided documentation supporting their use.

Target Drugs

Preferred Peginterferon	Non-Preferred Peginterferon
Pegasys® (peginterferon alfa-2a)	Pegintron® (peginterferon alfa-2b)

Oral Agents (NS3/4A protease inhibitors)
Incivek®™ (telaprevir)
Olysio™ (simeprevir)
Sovaldi™ (sofosbuvir)
Victrelis®™ (boceprevir)

FDA Approved Indications and Dosage[21,22,34,35]

Available Products	FDA Indication(s)	Dosage and Administration
Victrelis® (boceprevir)	For the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.	800 mg administered orally three times daily (every 7 - 9 hours) with food (a meal or light snack)
Incivek® (telaprevir)	In combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C (CHC) in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.	1125 mg taken 2 times a day (10-14 hours apart) with food (not low fat)

Available Products	FDA Indication(s)	Dosage and Administration
Olysio™ (simeprevir)	In combination with peginterferon alfa and ribavirin in chronic hepatitis C, genotype 1 patients with compensated liver disease (including cirrhosis). ▪ Efficacy of simeprevir in combination with peginterferon alfa and ribavirin is significantly reduced in patients with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to genotype 1a patients without the Q80K polymorphism. Screening for the presence of this polymorphism at baseline in STRONGLY recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism. ▪ Efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes simeprevir or other HCV protease inhibitors.	150 mg orally once daily with food
Sovaldi™ (sofosbuvir)	For the treatment of chronic hepatitis C as a component of a combination antiviral regimen ▪ Efficacy has been established in patients with genotype 1, 2, 3, or 4 including those with hepatocellular carcinoma meeting Milan criteria (awaiting transplant) and those with HCV/HIV-1 co-infection.	400 mg orally once daily

Dosing:[21,22]

- None of the agents is appropriate for monotherapy.
- Telaprevir and simeprevir should be started at the onset of therapy with duration of therapy of 12 weeks.
- Boceprevir should be initiated after 4 weeks of pegylated interferon and ribavirin. Duration of triple therapy thereafter is dependent on viral response at treatment week 8.
- The NS3/4A inhibitor agent has specific stopping rules.

POLICY

Prior Authorization Criteria for Approval

I. INITIAL EVALUTION

A. Initial Evaluation – DUAL THERAPY (peginterferon and ribavirin)

Preferred Peginterferon alfa (Pegasys) will be approved when ALL of the following are met:

1. The patient does not have any FDA labeled contraindications to therapy
   AND
2. ONE of the following:
   a. The patient has a diagnosis of chronic hepatitis C, genotype 2, 3, 4-6 confirmed by serological markers
      OR
   b. The patient has a diagnosis of chronic hepatitis C, genotype 1, confirmed by serological markers and is requesting dual therapy (peginterferon alpha plus ribavirin) instead of triple therapy (oral agent, peginterferon alpha, and ribavirin)
      OR
   c. The patient has a diagnosis of chronic hepatitis C, genotype 1, confirmed by serological markers and is requesting continued dual therapy after discontinuation of NS3 / 4A protease inhibitor oral agent as part of a triple therapy regimen

   AND
3. The patient has NOT received 24 months or more of total peginterferon therapy

Length of Approval: 24 months

B. Initial Evaluation – TRIPLE THERAPY (peginterferon, ribavirin, protease inhibitor)

Preferred Oral plus Preferred Peginterferon alfa (Pegasys) will be approved when ALL of the following are met:

1. The patient has a diagnosis of chronic hepatitis C genotype 1 infection confirmed by serological markers
   AND
2. The patient will receive triple therapy including an oral agent, peginterferon alfa (Pegasys) and ribavirin
   AND
3. The patient has a compensated liver (no evidence of clinical disease (e.g. absence of encephalopathy, ascites, or bleeding))
   AND
4. The patient does NOT have any FDA labeled contraindications, including coadministration with contraindicated medications (see table on page 10)
   AND
5. For OLYSIO, if the patient has subtype 1a, must NOT have the NS3 Q80K polymorphism
   AND
6. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:
   - Incivek: -1125 mg 2 times a day (10-14 hours apart)
     -1500 mg 2 times a day (10-14 hours apart) if coadministration with efavirenz
   - Olysio: -150 mg once daily
   - Victrelis: -800 mg 3 times a day (7-9 hours apart), starting after 4 weeks of peginterferon alfa and ribavirin therapy

   AND
7. The patient has not attempted a prior course of therapy with a treatment regimen that includes the requested agent or any other HCV NS3/4A protease inhibitor
   AND
8. The patient has not been administered the requested agent for longer than the maximum FDA labeled duration for total therapy:
   - Incivek and Olysio – 12 weeks
   - Victrelis – 44 weeks

Length of Approval: Incivek or Olysio plus peginterferon and ribavirin - 8 weeks*
Victrelis plus peginterferon and ribavirin - 16 weeks**

*HCV RNA level required at 4 weeks post first Incivek dose for evaluation of continued therapy

**HCV RNA level required at 8 weeks post first Victrelis dose (total treatment week 12) for evaluation of continued therapy

C. Initial Evaluation

***Nonpreferred* peginterferon (PegIntron) (DUAL or TRIPLE THERAPY)** will be approved when the criteria for the preferred peginterferon listed above are met AND ONE of the following is met:

1. The patient is currently being treated with the non-preferred agent (PegIntron)
   OR
2. The patient has a history of a trial of the preferred peginterferon (Pegasys)
   OR
3. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred peginterferon
   OR
4. The prescriber has submitted documentation in support of the use of the non-preferred peginterferon for the intended diagnosis

Length of Approval: Dual therapy (peginterferon + ribavirin) = 24 months
Triple therapy (peginterferon and ribavirin plus Incivek or Olysio) = 8 weeks

Triple therapy (peginterferon and ribavirin plus Victrelis) = 16 weeks

D. Initial Evaluation – Sovaldi (sofosbuvir)

1. The patient has a diagnosis of chronic hepatitis C infection confirmed by serological markers
   AND
2. Sofosbuvir will be used in a combination antiviral treatment regimen supported by FDA approved labeling or the AASLD guidelines (listed in Table 1 below)
   AND
   a. If genotype 1, treatment naïve requesting the combination of simeprivir and sofosbuvir, the patient has BOTH of the following:
      i. a METAVIR score of F3 (numerous septa, presumed fibrous) or F4 (cirrhosis)
      ii. Ineligible to receive peginterferon

   AND
3. The patient does NOT have any FDA labeled contraindications to sofosbuvir or the other agents used in the combination therapy
   AND
4. The patient will NOT be receiving Incivek (telaprevir) or Victrelis (boceprevir) concomitantly with sofosbuvir
   AND
5. If the patient has hepatocellular carcinoma the following are met:
   a. 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
   b. The patient has NO extrahepatic manifestations of cancer or evidence of vascular invasion of tumor

   AND
6. The dosing of sofosbuvir is within the FDA labeled dosage (400 mg daily)
   AND
7. If the treatment regimen includes simeprevir, the dosing of simeprevir is within the FDA labeled dosage (150 mg daily)

Table 1 AASLD Supported Sovaldi Containing Antiviral Regimens (Relapse to prior therapy should be treated the same as treatment naïve)

Genotype	Antiviral combination	SubGroup Designation[a] ([a]Patients are required to meet ALL subgroup requirements indicated by a ✓for the specified genotype and antiviral combination)			
		Naïve	Non-R	IFN eligible	IFN ineligible (Table 2)
1	Sovaldi + PEG + RBV	✓		✓	
	Sovaldi + Olysio ± RBV	✓			✓
	Sovaldi + RBV				
	Sovaldi + Olysio ± RBV		✓	One of the following: ✓	✓
	Sovaldi + PEG + RBV		✓	✓	
1a	Sovaldi + RBV		✓	One of the following: ✓	✓
	Sovaldi + PEG + RBV				
1b	Sovaldi + RBV		✓	One of the following: ✓	✓
	Sovaldi + PEG + RBV				
1 HIV Coinfect	Sovaldi + PEG + RBV	✓		✓	
	Sovaldi + RBV		✓		✓
	Sovaldi + Olysio + RBV		✓		✓
1 Post Transplant	Sovaldi + Olysio ± RBV	✓			
2*	Sovaldi + RBV	Any one of the following: ✓	✓	✓	✓
	Sovaldi + PEG + RBV		✓	One of the following: ✓	✓
2 Post Transplant	Sovaldi + RBV	✓			
3*	Sovaldi + RBV	Any one of the following: ✓	✓	✓	✓
	Sovaldi + PEG + RBV	✓		✓	
			✓	One of the following: ✓	✓
4	Sovaldi + RBV	One of the following: ✓	✓		✓
	Sovaldi + PEG + RBV	One of the following: ✓	✓	✓	
5 or 6	Sovaldi + PEG + RBV	✓		✓	
	Sovaldi + RBV		✓		✓
1-4 with hepato-cellular carcinoma or decompensated cirrhotics	Sovaldi + RBV	Any one of the following:			
		✓	✓	✓	✓

IFN = interferon, PEG = peginterferon, RBV = ribavirin, Non-R = non-responder
* Including HIV coinfected patients

Table 2

IFN 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 ▪ History of depression, or clinical features consistent with depression ▪ 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 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 3 Approval Duration

Genotype	Antiviral combination	Length of Approval
1	Sovaldi + PEG + RBV	12 weeks
	Sovaldi + Olysio ± RBV	12 weeks
	Sovaldi + RBV	24 weeks
	Sovaldi + Olysio ± RBV	12 weeks
	Sovaldi + PEG + RBV	12 weeks
1 Post Transplant	Sovaldi + Olysio ± RBV	12-24 weeks
1a	Sovaldi + RBV	24 weeks
	Sovaldi + PEG + RBV	Sovaldi 12 weeks PEG/RBV 24 weeks
1b	Sovaldi + RBV	24 weeks
	Sovaldi + PEG + RBV	Sovaldi 12 weeks PEG/RBV 24 weeks
1 – HIV Coinfect	Sovaldi + PEG + RBV	12 weeks
	Sovaldi + RBV	24 weeks
	Sovaldi + Olysio + RBV	12 weeks
2	Sovaldi + RBV	12 weeks
	Sovaldi + PEG + RBV	12 weeks
2 Post Transplant	Sovaldi + RBV	24 weeks
3	Sovaldi + RBV	24 weeks
	Sovaldi + PEG + RBV	12 weeks
3 Post Transplant	Sovaldi + RBV	24 weeks
4	Sovaldi + RBV	24 weeks
	Sovaldi + PEG + RBV	12 weeks
5 or 6	Sovaldi + PEG + RBV	12 weeks
	Sovaldi + RBV	24 weeks
1-4 with hepato-cellular carcinoma or decompensated cirrhotics	Sovaldi + RBV	48 weeks

II. Renewal Evaluations – (TRIPLE THERAPY)

A. Incivek or Olysio plus peginterferon and ribavirin

First Renewal – at 8 weeks (total treatment duration)

Incivek or Olysio plus peginterferon and ribavirin will be approved for renewal at 8 weeks when ALL of the following are met:

1. The patient has been previously approved for peginterferon and Incivek or Olysio
   AND
2. The patient's medication history indicates coadministration of peginterferon and ribavirin with Incivek or Olysio
   AND
3. The patient has had an HCV RNA level measured at **4 weeks** (total treatment duration) with a viral load less than 1000 IU/mL* or undetectable for Incivek and < 25 IU/mL* or undetectable for Olysio
   AND
4. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:
   - Incivek:
     -1125 mg 2 times a day (10-14 hours apart)
     -1500 mg 2 times a day (10-14 hours apart) if coadministration with efavirenz
   - Olysio:
     -150 mg once daily

*****Manufacturer recommends using the COBAS® TaqMan® assay when measuring HCV RNA levels.

Length of Approval:

Incivek or Olysio	4 weeks
peginterferon	8 weeks*

*HCV RNA level required at 12 weeks post first Incivek dose for evaluation of continued peginterferon therapy

B. Incivek or Olysio plus peginterferon and ribavirin
Second Renewal – at 16 weeks (total treatment duration)
Peginterferon will be approved for renewal at 16 weeks when ALL of the following are met:

1. The patient has been previously approved for peginterferon and Incivek or Olysio
   AND
2. The patient's medication history indicates coadministration of peginterferon and ribavirin
   AND
3. The patient has had an HCV RNA level measured at **12 weeks** (total treatment duration) with a viral load less than 1000 IU/mL* or undetectable for Incivek and < 25 IU/mL* or undetectable for Olysio

*****Manufacturer recommends using the COBAS® TaqMan® assay when measuring HCV RNA levels.

Length of Approval: peginterferon 32 weeks

C. Victrelis plus peginterferon and ribavirin
First Renewal – at 16 weeks (total treatment duration)
Victrelis plus peginterferon will be approved for renewal at 16 weeks when ALL of the following are met:

1. The patient has been previously approved for peginterferon and Victrelis
   AND
2. The patient's medication history indicates coadministration of peginterferon and ribavirin with Victrelis
   AND
3. The patient has had an HCV RNA level measured at **12 weeks** (total treatment duration) with a viral load less than 100 IU/mL* or undetectable
   AND
4. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:
   Victrelis:
   -800 mg 3 times a day (7-9 hours apart), starting after 4 weeks of peginterferon alfa and ribavirin therapy

*Manufacturer recommends using the COBAS® TaqMan® assay when measuring HCV RNA levels.

Length of Approval: Victrelis and peginterferon - 12 weeks

*HCV RNA level required at 20 weeks post first Victrelis dose (24 weeks total treatment duration) for evaluation of continued therapy

D. Victrelis plus peginterferon and ribavirin
Second Renewal – at 28 weeks (total treatment duration)
Victrelis plus peginterferon will be approved for renewal at 28 weeks when ALL of the following are met:

1. The patient has been previously approved for peginterferon and Victrelis
   AND
2. The patient's medication history indicates coadministration of peginterferon and ribavirin with Victrelis
   AND
3. The patient has had an HCV RNA level measured at **24 weeks** (total treatment duration) with a viral load less than 100 IU/mL* or undetectable
   AND
4. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:
   Victrelis:
   -800 mg 3 times a day (7-9 hours apart), starting after 4 weeks of peginterferon alfa and ribavirin therapy

*****Manufacturer recommends using the COBAS® TaqMan® assay when measuring HCV RNA levels.

Length of Approval: Victrelis and peginterferon - 20 weeks

Contraindications

Medication	Contraindications	Contraindicated medications
Incivek® (telaprevir)	Pregnancy and for men whose partners are pregnant (ribavirin), hypersensitivity, coadministration with highly CYP3A4/5 clearance dependent where elevated plasma levels could be serious or life threatening, concomitant use with potent CYP3A4/5 inducers where efficacy may be affected (see drugs listed at right)	alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, atorvastatin, lovastatin, simvastatin, Revatio / sildenafil, Adcirca (used for pulmonary arterial hypertension), pimozide, triazolam, midazolam (oral), St. John's Wort
Olysio™ (simeprevir)	Pregnancy and for men whose partners are pregnant (ribavirin), hypersensitivity	No contraindicated medications (see prescribing information for specific drug-drug interactions that may affect therapy)
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	None

Medication	Contraindications	Contraindicated medications
Victrelis® (boceprevir)	Pregnancy and for men whose partners are pregnant (ribavirin), hypersensitivity, coadministration with highly CYP3A4/5 clearance dependent where elevated plasma levels could be serious or life threatening, concomitant use with potent CYP3A4/5 inducers where efficacy may be affected (see drugs listed at right)	alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, lovastatin, simvastatin, drospirenone, Revatio / sildenafil, Adcirca (used for pulmonary arterial hypertension), pimozide, triazolam, midazolam (oral), St. John's Wort
Pegasys®	Hypersensitivity reactions, autoimmune hepatitis, hepatic decompensation (Child-Pugh score >6), neonates and infants, pregnancy, men whose partner is pregnant, hemoglobinopathies (e.g. thalassemia major, sickle-cell anemia), coadministration with didanosine	None
PegIntron®	Hypersensitivity reactions, autoimmune hepatitis, hepatic decompensation (Child-Pugh score >6), neonates and infants, pregnancy, men whose partner is pregnant, hemoglobinopathies (e.g. thalassemia major, sickle-cell anemia), creatinine clearance <50 mL/min	None

RATIONALE

Peginterferon for the Treatment of Hepatitis C

Patients who react positively to enzyme immunoassay for antibody to hepatitis C virus (HCV) or HCV RNA and have compensated liver disease are potential candidates for peginterferon therapy.[3] Proper duration of treatment is 12 continuous months for infection with HCV genotype 1, 4, 5, or 6 if there is a response to therapy at 12 weeks and six continuous months for genotype 2 and 3 which may be extended to 12 continuous months if there is evidence of cirrhosis, high viral load, or delayed response (response at 24 weeks versus 12 weeks)[4,5] There is evidence that patients considered slow responders (positive HCV RNA after 12 weeks of treatment but HCV RNA negative after 24 weeks) may benefit from a 72 week course of therapy.[6,7]

Comparative Clinical Trials of Peginterferon

Guidelines from the National Institutes of Health (NIH), National Institute for Health and Clinical Excellence (NICE), American Association for the Study of Liver Diseases (AASLD), and American Gastroenterological Association (AGA) also support a conclusion of similar efficacy between peginterferon products.[8-10]; however, all of the guidelines were written before the publication of several head-to-head, non-industry sponsored, investigator initiated, single center studies that found peginterferon α-2a to achieve higher sustained viral response rates (SVR) when compared to peginterferon α-2b.[12,13]

- Two independent, investigator-initiated, single-center, open-label, randomized trials compared the efficacy of peginterferon alfa-2a and peginterferon alfa-2b at standard doses and durations according to manufacture prescribing information. Both regimens were in combination with the ribavirin. The primary end point of both trials was SVR. Significantly

more patients in the peginterferon alfa-2a group than in the peginterferon alfa-2b group achieved an SVR in one trial (110/160 [68.8%] vs 87/160 [54.4%]; p=0.008)[12]. SVR was significantly higher in the peginterferon alfa-2a than in the peginterferon alfa-2b patients (66% vs 54%, respectively p=0.02) and 48% vs 32% in 222 HCV-1 and 4 patients (p=0.04), and 96% vs 82%, respectively, in the HCV 2 patients (p=0.01)[13] in another trial.

- A systematic review of head-to-head trials between the two PEG-IFN products assessed the benefits and harms of the 2 treatments (12 trials, n=5,008).[11]
  - Peginterferon alfa-2a significantly increased the number of patients who achieved a SVR versus peginterferon alfa-2b (8 trials: 47% vs 41%; risk ratio 1.11, 95% CI 1.04-1.19; p=0.004).
  - No significant differences in adverse effects were found between the two PEG-IFN products.

Peginterferon for the Treatment of Hepatitis B

The diagnosis of hepatitis B virus (HBV) is based on the presence of serological markers in the blood; hepatitis B viral DNA (HBV DNA), hepatitis B surface antigen (HBsAg) or hepatitis B 'e' antigen (HBeAg).[15] The AASLD 2009 guideline[16] for the treatment of hepatitis B virus recommends initiation of treatment with any of the seven approved antiviral medications but peginterferon, tenofovir, or entecavir are preferred. Advantages of peginterferon include a finite duration of treatment, a more durable response, and lack of resistant mutants. The duration of treatment with peginterferon for HBeAg positive HBV is 48 weeks. The European Association for the Study of Liver (EASL) 2009 practice guideline[17] also suggests peginterferon therapy for 48 weeks for both HBeAg positive and HBeAg negative HBV.

Peginterferon alfa-2a has an FDA approved indication for chronic hepatitis B while peginterferon alfa-2b is not FDA approved for chronic hepatitis B, however, there are studies that support its use for this indication.[18]

Peginterferon for the Treatment of Cancerous Conditions[19]

The off label use of peginterferon to treat various cancerous conditions including but not limited to hepatocellular carcinoma, gastrointestinal stromal tumors, kidney cancer, osteosarcoma, head and neck cancer, and melanoma has been investigated in several clinical trials. Peginterferon has been used as monotherapy, in combination with ribavirin, and in combination with other standard of care chemotherapy agents specific to the type of cancer being treated. Results of many clinical trials have either been preliminary or inconclusive.[20] The National Comprehensive Cancer Network (NCCN) Compendium lists peginterferon alfa 2a for the treatment of chronic myelogenous leukemia (CML) for patients unable to tolerate imatinib, dasatinib, or nilotinib or for post transplant patients who have relapsed as category 2A evidence. The same applies for peginterferon alfa 2-b with the added indication for melanoma (under the brand name Sylatron) as category 2B evidence.[28]

Oral Agents boceprevir, simeprevir, sofosbuvir, and telaprevir for the Treatment of Hepatitis C

Safety[21,22, 34, 35]

All of these agents are contraindicated in women that are pregnant or may become pregnant due to the required use in combination with ribavirin. Hepatitis C protease inhibitors (boceprevir,

simeprevir, and telaprevir) are metabolized via the CYP3A4/5 pathway and are contraindicated when used in combination with numerous agents that either inhibit or enhance the 3A4 pathway.

Contraindicated drugs include:

- Boceprevir: alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, ergot derivatives, cisapride, St. John's Wort, lovastatin, simvastatin, drospirenone, sildenafil, tadalafil, pimozide, triazolam, and oral midazolam
- Telaprevir: alfuzosin, rifampin, ergot derivatives, cisapride, St. John's Wort, lovastatin, simvastatin, atorvastatin, sildenafil, tadalafil, pimozide, triazolam, and oral midazolam

Hemoglobin should be monitored every 4 weeks while on therapy with these agents. Other adverse reactions seen in clinical trials include serious skin reactions (including Stevens-Johnson) and rash with telaprevir and neutropenia with boceprevir.

A drug interaction study showed that taking these agents in combination with certain HIV protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medications when used together and is not recommended. Other significant drug drug interactions can be found in the prescribing information. [21,22,29,34,35]

HIV Products	Victrelis (boceprevir)	Incivek (telaprevir)	Sovaldi (sofosbuvir)	Olysio (simeprevir)
Cobicisat-containing product				Increased plasma levels of simeprevir. Co-administration not recommended
Raltegravir	No dose adjustment for either agent		No dose adjustment needed	
Etravirine	Decrease in plasma trough concentrations for both agents. Avoid combination			
Atazanavir / ritonavir	Decreased steady state of atazanavir and ritonavir. Coadministration not recommended	Decreased steady state for telaprevir with increased steady state for atazanavir.		Co-administration with HIV protease inhibitors e.g. atazanavir, lopinavir, indinavir, etc.) may alter plasma concentrations of simeprevir. Co-administration not recommended.
Darunavir / ritonavir	Reduced steady state for boceprevir, darunavir, and ritonavir. Coadministration is not recommended.	Decreased steady state for telaprevir and darunavir. Coadministration not recommended	No dose adjustment needed	Increased plasma concentrations of simeprevir. Coadministration not recommended

HIV Products	Victrelis (boceprevir)	Incivek (telaprevir)	Sovaldi (sofosbuvir)	Olysio (simeprevir)
Fosamprenavir / ritonavir		Decreased steady state for telaprevir and amprenavir. Coadministration not recommended.		Co-administration with HIV protease inhibitors e.g. atazanavir, lopinavir, indinavir, etc.) may alter plasma concentrations of simeprevir. Co-administration not recommended.
Lopinavir / ritonavir	Reduced steady state for boceprevir, lopinavir, and ritonavir. Coadministration is not recommended.	Decreased steady state for telaprevir with no effect on steady state for lopinavir. Coadministration not recommended.		Co-administration with HIV protease inhibitors e.g. atazanavir, lopinavir, indinavir, etc.) may alter plasma concentrations of simeprevir. Co-administration not recommended.
Tipranavir / ritonavir			Coadministration of sofosbuvir with tipranavir/ritonavir is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.	
Ritonavir	Decreased concentrations of boceprevir			Increased plasma concentrations of simeprevir. Coadministration not recommended
Efavirenz		Reduced steady state for both telaprevir and efavirenz	No dose adjustment needed	Significantly decreases plasma concentrations of simeprevir. Co-administration not recommended
Tenofovir		Increase tenofovir exposure. Increase clinical and lab monitoring. Discontinue in those developing tenofovir	No dose adjustment needed	

HIV Products	Victrelis (boceprevir)	Incivek (telaprevir)	Sovaldi (sofosbuvir)	Olysio (simeprevir)
		toxicities.		

Efficacy[21-27,34,35]

Simeprevir
The efficacy and safety of simeprevir for the treatment of chronic hepatitis C in genotype 1 patients was evaluated in three phase 3 trials (QUEST 1, QUEST 2, and PROMISE) and a Phase 2b trial (ASPIRE). QUEST 1 and 2 were treatment naïve patients, PROMISE included relapsed patients after prior interferon-based therapy and ASPIRE evaluated prior partial and null responders to previous interferon based therapy. All were randomized controlled trials against peginterferon alfa and ribavirin plus placebo. The primary efficacy endpoint in all trials was the sustained viral response (SVR) at planned end of treatment. For QUEST 1 and 2 SVR was defined as HCV RNA < 25 IU/mL detectable of undetectable at 12 weeks. For PROMISE SVR was defined as HCV RNA < 25 IU/mL at week 24.

Results were reported by subtype (genotype 1a or genotype 1b). The subtype of 1a was then broken out by results for patients with and without the NS3 Q80K polymorphism. Pooled results showed significantly higher SVR rates in patients treated with simeprevir (in combination with peginterferon alfa and ribavirin) compared to placebo (in combination with peginterferon alfa and ribavirin) EXCEPT for patients with the subtype 1a WITH the NS3 Q80K polymorphism. Labeling recommends baseline assessment for the Q80K polymorphism and those positive be considered for an alternative therapy.

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 peg and ribavirin) (>20%) and occurring with at least 3% higher frequency compared to subjects receiving placebo (also in combination with peg and ribavirin) include rash (including photosensitivity), pruritus and nausea.35

Boceprevir and Telaprevir
The efficacy and safety of telaprevir was evaluated in three (ADVANCE, ILLUMINATE, and REALIZE), phase 3 trials in adult patients with hepatitis C (genotype 1). The efficacy and safety of boceprevir was evaluated in two phase 3 clinical trials (HCV SPRINT 2 and HCV RESPOND 2). For both drugs, only patients with genotype 1 were treated – either treatment-naïve or patients who had failed a previous course of HCV therapy.

Telaprevir, in combination with peginterferon and ribavirin, was given for 8 to 12 weeks then followed by treatment with peginterferon and ribavirin. Treatment-naïve patients were treated for a total treatment duration ranging from 24 weeks up to 48 weeks. In the IILUMINATE trial, the viral cure rates found that there was no benefit to extending telaprevir based therapy to 48 weeks for the majority of patients.

Both boceprevir trials included a four week lead-in phase of peginterferon plus ribavirin (without boceprevir). Then boceprevir was added for the remainder of the study. For treatment naïve

patients, the 4 week lead-in was followed by the triple combination of boceprevir, peginterferon, ribavirin– treatment duration was guided by on-treatment response–either 28 weeks or 48 weeks. For treatment failure patients, the 4 week lead-in phase was followed by the triple combination of boceprevir, peginterferon, ribavirin– treatment duration was guided by on-treatment response–either 36 weeks or 48 weeks.

In phase 3 clinical studies for both drugs, sustained viral response (SVR) was significantly higher with protease inhibitors in combination with peginterferon and ribavirin than peginterferon plus ribavirin alone in both treatment naïve and in patients who failed prior therapy

Provisional guidance for the use of HCV protease inhibitors in the HIV co-infected population published by Clinical Infectious Disease recommends the following[33]:

- Peginterferon and ribavirin remain the standard of care for HCV genotype 2, 3, or 4 HCV infection or in patients with interactions with HCV PIs that cannot be eliminated or managed.
- Some genotype 1 HCV/HIV co-infected patients should be treated with HCV PIs in combination with PEG/RBV.
- HIV infection should be controlled before treatment with HCV PIs in combination with PEG/RBS. HIV titers should be monitored closely when HCV PIs are used with antiretroviral (ART) therapy.
- Increase dosing of telaprevir of 1125 mg three times a day (7-9 hours apart) when coadministered with efavirenz.
- Until research demonstrates safety, boceprevir should not be used with efavirenz, etravirine, or nevirapine.
- Avoid boceprevir use with ritonavir-boosted lopinavir, atazanavir, or darunavir.

Sofosbuvir and Simeprevir Combination

The combination of these agents is being evaluated in an ongoing phase 2 clinical study of sofosbuvir plus simeprevir with or without RBV for 12 or 24 weeks. The study enrolled 2 cohorts: cohort 1 is comprised of prior null responders to PEG/RBV with Metavir fibrosis stage 0 or 2; Cohort 2 is treatment naïve or prior null responder patients with Metavir fibrosis stage 3 or 4. The 12-week SVR rates for cohort 1 for patients treated with RBV was 96% and 93% for those without RBV. The 24-week treatment group had SVR12 rates of 79.3% and 93% for patient with and without RBV use respectively. There were not any viral breakthroughs in cohort 1 but 3 patients had relapse after stopping therapy. Preliminary SVR4 rates for cohort 2 the 12 week regimen group were 100% in treatment naïve patients irrespective of ribavirin use and 100% and 93.3% in prior null responders treated with and without RBV respectively.[36]

The combination is well tolerated with approximately 2.4% of patients discontinuing due to adverse events. Sofosbuvir resistance-associated variants have not been detected.[36]

Clinical Guidelines[27,30]

The European Association For The Study of The Liver (EASL) clinical practice guidelines recommend the following regarding the use of the direct acting antiviral agents:

1. Direct acting agents should only be used according to package labeling.

2. The following potential challenges of using HCV protease inhibitors in combination with pegylated interferon alpha (PEG-INFa) and ribavirin should be considered:

a. Rapid emergence of resistance particularly in non-responder patients, non-adherent patients, and patients not able to tolerate optimal doses of PEG-INFa and ribavirin.
b. More strict and frequent monitoring of HCV RNA.
c. Lower response rates to triple therapy in patients with advanced liver fibrosis.
d. Adherence to recommended stopping rules for the antiviral agent and/or the entire treatment regimen.
e. Additional side effects associated with protease inhibitor therapy.

American Association for the Study of Liver Diseases (AASLD, 2013) guidelines recommend the following in treatment naïve patients (see guidelines for alternative regimen recommendations):[36]

1. Genotype 1IFN eligible - sofosbuvir in combination with interferon (IFN) and ribavirin (RBV)
2. Genotype 1 IFN ineligible - sofosbuvir in combination with simeprevir with or without RBV irrespective of subtype.
3. Genotype 2 and 3 regardless of IFN eligibility - sofosbuvir in combination with RBV.
4. Genotype 4 IFN ineligible - sofosbuvir in combination with RBV.
5. Genotype 5 and 6 IFN eligible – sofosbuvir in combination with IFN and RBV

AASLD guidelines recommend the following for previous failures of interferon (IFN) and ribavirin (RBV):[37]

1. Genotype 1 IFN/RBV only nonresponder patients – sofosbuvir in combination with simeprevir, with or without RBV irrespective of IFN eligibility or subtype.
2. Genotype 1a IFN/RBV/DAA (telaprevir or boceprevir) failures – sofosbuvir for 12 weeks in combination with IFN and RBV for 24 weeks.
3. Genotype 1b IFN/RBV/DAA (telaprevir or boceprevir) failures – sofosbuvir for 12 weeks in combination with IFN and RBV for 12-24 weeks.
4. Genotype 2 IFN/RBV nonresponders – sofosbuvir plus RBV.
5. Genotype 3 IFN/RBV nonresponders – sofosbuvir plus RBV.
6. Genotype 4, 5 and 6 IFN/RBV nonresponders – sofosbuvir plus RBV.

AASLD guidelines recommend the following for special populations:[38]

1. HIV/HCV coinfected genotype 1 naïve and prior relapsers IFN eligible – sofosbuvir plus PEG and RBV for 12 weeks irrespective of subtype
    a. IFN ineligible – sofosbuvir plus RBV for 24 weeks
2. HIV/HCV coinfected genotype 1 naïve and prior relapsers IFN ineligible – sofosbuvir plus simeprevir ± RBV for 12 weeks
3. HIV/HCV coinfected genotype 1 treatment experienced with PEG/RBV nonresponse (irrespective of IFN eligibility) – sofosbuvir plus simeprevir ± RBV for 12 weeks
4. HIV/HCV coinfected genotype 1 previous DAA nonresponse – treat as monoinfected
5. HIV/HCV coinfected genotype 2 or 3 – use regimen for HCV monoinfected
    a. Genotype 2 – sofosbuvir + RBV for 12 in naïve and experienced.
    b. Genotype 3 – sofosbuvir + RBV for 24 weeks
6. HIV/HCV coinfected genotypes 4, 5, or 6 – treat as monoinfected
7. Naïve patients with compensated cirrhosis (including those with hepatocellular carcinoma) treat same as those without cirrhosis
8. If treating decompensated cirrhosis patients – sofosbuvir + RBV for up to 48 weeks
9. Post liver transplant, genotype 1 – sofosbuvir + simeprevir ± RBV for 12 to 24 weeks
10. Post liver transplant genotypes 2 or 3 – sofosbuvir + RBV for 24 weeks

Guidelines advise for patients with genotype 1a, detection of the Q80K polymorphism does not preclude treatment with simeprevir in combination with sofosbuvir because the SVR rate was higher in patients with genotype 1a/Q80K infection.[36] Guidelines define IFN ineligible 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
- History of depression, or clinical features consistent with depression
- 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 as intolerance to the drug and/or excipients, not the route of administration administration including patients who have previously discontinued therapy with IFN due to adverse events (e.g. hypersensitivity, anaphylaxis, severe rash, severe anemia, etc.).

The guidelines address the use of simeprevir as it pertains to testing for the Q80K polymorphism. "For patients infected with genotype 1a HCV, baseline resistance testing for the Q80K polymorphism may be considered. However, in contrast to using simeprevir to treat a genotype 1a HCV patient with PEG/RBV when the mutation markedly alters the probability of an SVR, the finding of the Q80K polymorphism does not preclude treatment with simeprevir and sofosbuvir, because the SVR rate was high in patients with genotype 1a/Q80K infection (SVR12 rate for cohort 1 was 86% [24 of 28 patients]; SVR4 rate for cohort 2 was 90% [10 of 11 patients]). To date, virologic failure has not been observed in patients in either cohort infected with HCV genotype 1b and with HCV genotype 1a in the absence of the Q80K polymorphism. Thus Q80K testing can be considered but is not strongly recommended."[36]

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

There are no specific HCPCS codes for the drugs listed in this policy.

REVISIONS

03-28-2012	Policy added to the bcbsks.com web site. Policy was effective January 1, 2012.
07-01-2012	Format and order of policy revised
	In Policy section: In Hepatitis B – Through Preferred Agent ▪ Revised A from: "Pegasys or PegIntron will be approved when Peginterferon is being prescribed for the treatment of a cancerous or pre-cancerous condition." to: "Pegasys or PegIntron will be approved when ONE of the following is met: 1. Peginterferon is being prescribed for the treatment of chronic myelogenous leukemia

	(CML) OR 2. The use of the requested agent is for an oncology indication that is supported by compendia (NCCN Compendium™ level of evidence 1, 2A, or 2B, AHFS, DrugDex, Clinical Pharmacology) or the prescriber has submitted additional documentation supporting the requested therapeutic use (approval by the Clinical Review Pharmacist required)." ▪ In Length of Approval revised: "Indefinite for treatment of a cancerous or pre-cancerous condition" to: "Indefinite for treatment of CML or oncology indication as supported by compendia" <u>Hepatitis C Agents (Pegasys, PegIntron, Incivek, Victrelis) Prior Authorization</u> ▪ Removed from I. B. 3. "(Child-Pugh score <6)" to read "The patient has compensated liver disease" ▪ Removed from C 2 c and I C 4 "which has been reviewed and approved by the Clinical Review pharmacist" as all components of the policy are subject to review and approval by the Clinical Review pharmacist. ▪ Removed "plus Incivek" from II. B. to read, "Peginterferon will be approved..."
	Rationale section added
01-01-2013	(Posted to the web site 11-30-2012)
	In Title section: ▪ Revised title from "Hepatitis B / Hepatitis C Agents Prior Authorization Criteria" to "Hepatitis B / Oncology and Hepatitis C Agents"
	In Hepatitis B–Through Preferred Agent Description section: ▪ Updated description ▪ Added FDA Approved Indications and Dosage chart
	In Hepatitis B – Through Preferred Agent Policy section: ▪ In I B 1 revised months of total therapy from 24 to 18 to read, "1. The patient has not been administered peginterferon for more than 18 months of total therapy"
	In Hepatitis C Agent–Through Preferred Peginterferon Agent Description section: ▪ Added FDA Approved Indications and Dosage chart ▪ Added Dosing bullets
	In Hepatitis C Agent–Through Preferred Peginterferon Agent Policy section: ▪ Removed criteria I A 1 d of, "The patient has a diagnosis of chronic hepatitis C (any genotype) with HIV co-infection" ▪ Revised II B 3 from, "The patient has compensated liver disease" to "The patient has a compensated liver (no evidence of clinical disease e.g. absence of encephalopathy, ascites, or bleeding)" ▪ Removed criteria II B 5 of, "The patient does NOT have HIV/AIDs" ▪ Added to II B 6 "or provisional guideline" to read, "The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:" ▪ Added to II B 6 Incivek the dose of, "-1125 mg 3 times a day (7-9 hours apart) when coadministered with efavirenz" ▪ Added to II A the criteria of, "2. The patient's medication history includes coadministration with peginterferon and ribavirin with Incivek AND" ▪ Added to II A the criteria of, "4. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent: ▪ Incivek: -750 mg 3 times a day (7-9 hours apart); -1125mg 3 times a day (7-9 hours apart) when coadministered with efavirenz" ▪ Added to II B the criteria of, "2. The patient's medication history includes coadministration of peginterferon and ribavirin with Victrelis AND" ▪ Added to II C and II D the criteria of, "2. The patient's medication history includes coadministration with peginterferon and ribavirin with Victrelis AND" ▪ Added to II C and II D the criteria of, "4. The dose is within the FDA labeled or provisional guideline dosage for the requested oral agent:

	▪ Victrelis: -800 mg 3 times a day (7-9 hours apart), starting after 4 weeks of peginterferon alfa and ribavirin therapy" ▪ Added to the Contraindicated Medications chart "sildenafil" to read, "...Revatio/sildenafil,..."
	Updated Rationale section
	Updated References
01-01-2014	In I. Hepatitis B / Oncology Description section: ▪ Updated FDA Approved Indications and Dosage chart
	In I. Hepatitis B / Oncology Policy section: ▪ In Item A, B, and C added, "The patient does not have any FDA labeled contraindications to therapy" and revised accompanying wording accordingly.
	In II Hepatitis C Agents Header and Description section: ▪ Revised "II. Hepatitis C Agents – Through Preferred Peginterfergon Agent" to read, "II. Hepatitis C Agents – Through Preferred Hepatitis C Agents" ▪ Updated Description
	In II Hepatitis C Agents Policy section: ▪ In Item I A changed "BOTH of the following are met:" to "ALL of the following are met:" ▪ In Item I A added, "The patient does not have any FDA labeled contraindications to therapy" and revised accompanying wording accordingly. ▪ In Item I B revised "(peginterferon, ribavirin, and Incivek or Victrelis) Oral plus Preferred Peginterferon alfa (Pegasys)..." to "(peginterferon, ribavirin, protease inhibitor Preferred Oral plus Preferred Peginterferon alfa (Pegasys)..." ▪ In Item I B 4 revised "The patient is NOT receiving a contraindicated medication (see table on page 10)" to read "The patient does NOT have any FDA labeled contraindications, including coadministration with contraindicated medications (see table on page 10)" ▪ In I C added "(DUAL or TRIPLE THERAPY)" to read, "Nonpreferred peginterferon (PegIntron ((DUAL or TRIPLE THERAPY)" ▪ In II added "(TRIPLE THERAPY) to read "Renewal Evaluations - (TRIPLE THERAPY)" ▪ In II A 3 and II B 3 added "or undetectable" to read, "...with a viral load less than 100 IU/mL* or undetectable" ▪ In B 3 removed "with Victrelis" ▪ In II C 3 and II D 3 added "or undetectable" to read, "...with a viral load less than 100 IU/mL* or undetectable" ▪ Updated Contraindicated Medications chart
	Rationale updated
	Added Coding section and "There are no specific HCPCS codes for the drugs listed in this policy."
	References updated
02-10-2014	Title updated to add: "Olysio™ (simeprevir), Sovaldi™/sofosbuvir"
	▪ In Description section II Hepatitis C Agents – Through Preferred Hepatitis C Agents updated ▪ Description updated ▪ Target Drugs – Oral Agents chart updated ▪ FDA Approved Indications and Dosage updated ▪ Dosing updated
	In Policy section II HEPATITIS C AGENTS - Through Preferred Hepatitis C Agents: ▪ Added Item I B 5, "For OLYSIO, if the patient has subtype 1a, must NOT have the NS3 Q80K polymorphism AND" ▪ Revised Item I B 6 to change Incivek dosages from, "-750 mg 3 times a day (7-9 hours apart); -1125 mg 3 times a day (7-9 hours apart) if coadministration with efavirenz" to "-

1125 mg 2 times a day (10-14 hours apart; -1500 mg 2 times a day (10-14 hours apart) if coadministration with efavirenz" and added, " Olysio:-150 mg once daily"

- Added to Item I B 8, "and Olysio" to read, "Incivek and Olysio"
- Added to Item I B Length of Approval, "or Olysio" to read "Incivek or Olysio"
- Revised Item I C Length of Approval from "Triple therapy (peginterferon + ribavirin + Incivek) = 8 weeks" and "Triple therapy (peginterferon + ribavirin + Victrelis) = weeks" to "Triple therapy (peginterferon plus Incivek or Olysio) = 8 weeks" and "Triple therapy (peginterferon plus Victrelis) = 16 weeks"
- Added section I D "Initial Evaluation – Sovaldi (sofosbuvir)

1. The patient does not have any FDA labeled contraindications AND
2. ONE of the following:
   a. The patient has a diagnosis of hepatitis C genotype 2 or 3 confirmed by serological markers AND will receive concomitant ribavirin OR
   b. The patient has a diagnosis of hepatitis C genotype 4 confirmed by serological markers AND will receive concomitant peginterferon alfa and ribavirin OR
   c. The patient has a diagnosis of hepatitis C genotype 1 confirmed by serological markers AND ONE of the following:
      1) The patient will receive concomitant peginterferon alfa and ribavirin OR
      2) The patient is ineligible to receive peginterferon alfa AND will receive concomitant ribavirin
   d. The patient has hepatitis C genotype 1 through 4 confirmed by serological markers and hepatocellular carcinoma AND ALL of the following:
      1) The patient is pre-transplant AND
      2) ONE of the following:
         a) The patient has a single tumor 5 cm or less in diameter OR
         b) The patient has up to 3 tumors with each being 3 cm or less in diameter AND
      3) The patient has NO extrahepatic manifestations of cancer or evidence of vascular invasion of tumor AND
3. The patient will NOT be receiving an NS3/4 A protease inhibitor (i.e. Incivek, Olysio, or Victrelis) at the same time as Sovaldi AND
4. The dose is within the FDA labeled dose"

- Added Length of approval chart

Genotype	Combination Medication	Length of Approval
1 or 4	Pegylated interferon AND ribavirin	12 weeks
1	Ribavirin ONLY	24 weeks
2	Ribavirin	12 weeks
3	Ribavirin	24 weeks
Hepatocellular Carcinoma -Pre-transplant	Ribavirin	48 weeks

- Added section I E "Initial Evaluation

Nonpreferred peginterferon will be approved when the criteria for the preferred peginterferon listed above are met AND ONE of the following is met:

1. The patient is currently being treated with the non-preferred agent OR
2. The patient has a history of a trial of the preferred peginterferon OR
3. The patient has an FDA labeled contraindication, documented intolerance, or hypersensitivity to the preferred peginterferon, OR
4. The prescriber has submitted documentation in support of the use of the non-preferred peginterferon, for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist "

- Added Length of approval chart

Genotype	Combination Medication	Length of Approval
1 or 4	Pegylated interferon AND ribavirin	12 weeks

<table>
<tr><td></td><td>
<table>
<tr><td>1</td><td>Ribavirin ONLY</td><td>24 weeks</td></tr>
<tr><td>2</td><td>Ribavirin</td><td>12 weeks</td></tr>
<tr><td>3</td><td>Ribavirin</td><td>24 weeks</td></tr>
<tr><td>Hepatocellular Carcinoma -Pre-transplant</td><td>Ribavirin</td><td>48 weeks</td></tr>
</table>
▪ Added to Items II A 1 and II A 2 "or Olysio" to read, "Incivek or Olysio"
▪ Added to Item II A 3 "for Incivek and < 25 IU/mL* or undetectable for Olysio" to read, "...with a viral load less than 1000 IU/mL* or undetectable for Incivek and < 25 IU/mL* or undetectable for Olysio"
▪ Revised Item II A 4 to change Incivek dosages from, "-750 mg 3 times a day (7-9 hours apart); -1125 mg 3 times a day (7-9 hours apart) if coadministration with efavirenz" to "-1125 mg 2 times a day (10-14 hours apart; -1500 mg 2 times a day (10-14 hours apart) if coadministration with efavirenz" and added, "Olysio:-150 mg once daily"
▪ Added to Item II A Length of Approval, "or Olysio" to read "Incivek or Olysio"
▪ Added to Items II B 1 "or Olysio" to read, "Incivek or Olysio"
▪ Added to Item II B 3 "or undetectable for Incivek and < 25 IU/mL* or undetectable for Olysio" to read, "with a viral load less than 1000 IU/mL* or undetectable for Incivek and < 25 IU/mL* or undetectable for Olysio"
▪ Updated Contraindicated Medications chart to add Olysio and Sovaldi.</td></tr>
<tr><td></td><td>Rationale section updated</td></tr>
<tr><td></td><td>References updated</td></tr>
<tr><td>02-11-2014</td><td>▪ Updated Prior Authorization form link for Incivek Victrelis Olysio
▪ Established Prior Authorization form link for Sovaldi</td></tr>
<tr><td>04-22-2014</td><td>In Description section:
▪ Description section II HEPATITS C AGENTS – Through Preferred Hepatitis C Agents updated
▪ Dosing information updated</td></tr>
<tr><td></td><td>In Policy section II HEPATITIS C AGENTS - Through Preferred Hepatitis C Agents:
▪ In I B Length of Approval added "and ribavirin" to read, "Incivek or Olysio plus peginterferon and ribavirin" and "Victrelis plus peginterferon and ribavirin"
▪ In I C Length of Approval added "and ribavirin" to read, "Triple therapy (peginterferon and ribavirin plus Incivek or Olysio)" and "Triple therapy (peginterferon and ribavirin plus Victrelis)"
▪ In I D Initial Evaluation – Sovaldi (sofosbuvir) replaced current language of:
"1. The patient does not have any FDA labeled contraindications AND
2. ONE of the following:
a. The patient has a diagnosis of hepatitis C genotype 2 or 3 confirmed by serological markers AND will receive concomitant ribavirin OR
b. The patient has a diagnosis of hepatitis C genotype 4 confirmed by serological markers AND will receive concomitant peginterferon alfa and ribavirin OR
c. The patient has a diagnosis of hepatitis C genotype 1 confirmed by serological markers AND ONE of the following:
1) The patient will receive concomitant peginterferon alfa and ribavirin OR
2) The patient is ineligible to receive peginterferon alfa AND will receive concomitant ribavirin
d. The patient has hepatitis C genotype 1 through 4 confirmed by serological markers and hepatocellular carcinoma AND ALL of the following:
1) The patient is pre-transplant AND
2) ONE of the following:
a) The patient has a single tumor 5 cm or less in diameter OR
b) The patient has up to 3 tumors with each being 3 cm or less in diameter AND
3) The patient has NO extrahepatic manifestations of cancer or evidence of vascular invasion of tumor AND</td></tr>
</table>

	3. The patient will NOT be receiving an NS3/4 A protease inhibitor (i.e. Incivek, Olysio, or Victrelis) at the same time as Sovaldi AND 4. The dose is within the FDA labeled dose" WITH: "1. The patient has a diagnosis of chronic hepatitis C infection confirmed by serological markers AND 2. Sofosbuvir will be used in a combination antiviral treatment regimen supported by FDA approved labeling or the AASLD guidelines (listed in Table 1 below) AND 3. The patient does NOT have any FDA labeled contraindications to sofosbuvir or the other agents used in the combination therapy AND 4. The patient will NOT be receiving Incivek (telaprevir) or Victrelis (boceprevir) concomitantly with sofosbuvir AND 5. If the patient has hepatocellular carcinoma the following are met: a. 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 b. The patient has NO extrahepatic manifestations of cancer or evidence of vascular invasion of tumor AND 6. The dosing of sofosbuvir is within the FDA labeled dosage (400 mg daily) AND 7. If the treatment regimen includes simeprevir, the dosing of simeprevir is within the FDA labeled dosage (150 mg daily)" ▪ For item I D, added Table 1 entitled "AASLD Supported Sovaldi Containing Antiviral Regiments" ▪ For item I D, added Table 2 which defines "INF ineligible" ▪ For item I D, replaced Length of approval table with Table 3 "Approval Duration" with the following columns: Genotype, Antiviral combination, and Length of Approval. ▪ In II A added "and ribavirin" to read in the sub-title, "Incivek or Olysio plus peginterferon and ribavirin" and in the introduction of the criteria, "Incivek or Olysio plus peginterferon and ribavirin will be approved…" ▪ In II B added "or Olysio" and "and ribavirin" to read in the sub-title, "Incivek or Olysio plus peginterferon and ribavirin" ▪ In II C and II D added "and ribavirin" to read, "Victrelis plus peginterferon and ribavirin"
	Rationale section updated
	References updated
06-15-2014	Policy posted August 12, 2014. Policy effective July 15, 2014.
	In Description section: ▪ Description section II HEPATITS C AGENTS – Through Preferred Hepatitis C Agents updated Dosing information updated
	In Policy section II HEPATITIS C AGENTS - Through Preferred Hepatitis C Agents: ▪ In Item D 2 added "a. If genotype 1, treatment naïve requesting the combination of simeprivir and sofosbuvir, the patient has BOTH of the following: i. a METAVIR score of F3 (numerous septa, presumed fibrous) or F4 (cirrhosis) ii. Ineligible to receive peginterferon AND" ▪ In Table 1 added Genotype, Antiviral combination and SubGroup Designation for 1 HIV Coinfect, 1 Post Transplant, 2 Post Transplant. ▪ In Table 1 updated Genotype 5 or 6 adding an Antiviral combination ▪ In Table 1 added "or decompensated cirrhotics" to the Genotype to read, "1-4 with hepato-cellular carcinoma or decompensated cirrhotics" ▪ In Table 1 added asterisks to 2 and 3 meaning "Including HIV coinfected patients" ▪ Following Table 2 added "including patients who have previously discontinued therapy with IFN due to adverse events (e.g. hypersensitivity, anaphylaxis, severe rash, severe anemias, etc.)." to correct and incomplete sentence. ▪ In Table 3 added Genotype, Antiviral combination and Length of Approval for 1 Post

	Transplant, 1 HIV Coinfect, 2 Post Transplant, 3 Post Transplant. ▪ In Table 3 updated Genotype 5 or 6 adding an Antiviral combination and related length of approval. ▪ In Table 3 added "or decompensated cirrhotics" to the Genotype to read, "1-4 with hepato-cellular carcinoma or decompensated cirrhotics"
	In Rationale section: ▪ Updated supporting clinical information. ▪ Added AASLD guidelines for special populations
	References updated

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